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RECURRENT ASIAN INFLUENZA IN AN INDUSTRIAL POPULATION * †

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AN epidemic of influenza may disable a significant number of workers in an industrial plant and seriously curtail its operation. At present, vaccination offers the only means of offsetting these consequences. Since acceptability of the vaccine dictates the amount of its use in a civilian population, this factor must be considered along with the protective effect of the vaccine in evaluating the degree of success in a program of control. Accordingly, it was of interest to investigate two occurrences of influenza A2 in an industrial population that had been offered influenza immunization on an annual basis since 1957.

In the winter of 1960, an outbreak of Asian influenza recurred in an industrial population which had been affected by the 1957–1958 epidemic. Since the employees of the plant were subjects of an acute respiratory disease study which encompassed both epidemics, an opportunity was provided for the derivation of clinical, laboratory, and epidemiologic information on Asian influenza. The two episodes described in this paper exhibited different patterns of involvement in the worker population, as reflected by attack rates and the impact of the disease on sickness absenteeism. Observations were made on the protective effects of immunization programs. Results were also analyzed statistically to determine whether attacks of influenza experienced during the first epidemic provided immunity during

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the second, and whether vaccine administered to workers at intervals between 1957 and 1960 provided protection during the 1960 outbreak. Except for immunization during the epidemic year, it will be shown that there was an absence of protective effect from a previous attack of Asian influenza and/or previous vaccination on the individual's susceptibility to the disease in 1960.

Methods

Clinical and Epidemiologic Observation: From July, 1957, through the spring of 1960, data on acute respiratory illnesses were gathered from employees of a large oil refinery and petrochemical plant located in Baton Rouge, Louisiana. The plant has an average population of approximately 6,200 employees who reside in Baton Rouge (metropolitan area population 250,000) or nearby communities of southcentral Louisiana. The workers' age range was 20 to 65 years, the average being 46. Females constituted less than 5% of the employees, and were excluded from the study. Approximately 29% of the male workers were salaried, 43% were maintenance, and 28% were production wage earners.

Refinery medical department personnel collected historical and clinical information on all respiratory illnesses in 1,000 of these employees. Appropriate questionnaires were devised for the recording of information, which was coded for electronic data processing machine analysis. Standard criteria for the clinical diagnosis of influenza included: fever above 100.4° F., prominent malaise or muscular aches, and associated upper respiratory symptoms. Essentially, all employees so afflicted were disabled for work, and were seen in the company medical department during or immediately after the illness. Medical reports were obtained in most cases from attending physicians or by home visits to patients by the plant visiting nurse. In addition to the prospective plan of the study and the recording of pertinent disease symptoms and findings on a current basis, an interview between a plant physician and each patient served to corroborate and classify the information in retrospect.

Laboratory Studies: For virus isolation, garglings were obtained with 0.5% lactalbumin hydrolysate in Hanks' solution as the vehicle. Specimens were refrigerated for one to three days and then stored at —70° C. All were passaged twice in the amniotic sac of 10 to 11-day embryonated eggs with a four day incubation period. Some were also passed twice in monkey kidney cultures using technics previously described.[1] Serologic determinations were done with sera treated with broth culture filtrates of *Vibrio cholerae* (receptor destroying enzyme), and antibody was titrated by hemagglutination-inhibition. A tissue culture line of Asian virus (influenza A2/NO1/57) isolated in New Orleans in 1957 and propagated in monkey kidney cultures was used for this purpose.[1] Egg lines of influenza A-prime (A1/Denver/57), influenza B/GL1760/54, and a strain isolated from an airman at Keesler Air Force Base (influenza B/KAFB302/59), were also

employed. Pharyngeal swabbings from selected cases were cultured on 5% sheep's blood agar plates for the identification of bacterial pathogens, particularly beta hemolytic streptococci.

Vaccine and Appraisal of Effectiveness: Standard influenza vaccine containing inactivated influenza viruses that had been propagated in the embryonated egg was obtained from commercial sources during September of each year. Vaccine was offered to employees each fall and winter of the three-year period. Monovalent Asian influenza vaccine, 200 chick cell-agglutination (CCA) U/ml. was administered in dosage of 0.1 to 0.2 ml. intradermally, from late August, 1957, until February, 1958. A second injection was given at least six weeks after the first (65% of workers received a single injection and 34% received two injections of the vaccine). The following year 0.5 ml. of polyvalent influenza vaccine, 500 CCA U/ml., was administered subcutaneously to 43% of the worker population, 30% receiving two doses and 13% a single injection. This vaccine contained 200 CCA U/ml. of Asian virus. In October, 1959, a single injection of 0.5 ml. polyvalent influenza vaccine was given subcutaneously to 32% of employees. Vaccine type, dosage, route, and date of administration were recorded and coded for machine correlation with sickness and absenteeism experience. Consequently, physicians were able to record clinical observations without knowing the vaccine status of an individual, thus avoiding bias in the classification of disease.

Statistical Analysis of Recurrent Influenza: Six hundred cases of typical influenza from the 1960 outbreak were matched with 600 individuals free of significant respiratory disease during the epidemic period with respect to age, service, and job assignment. The information as to each individual's prior experience with influenza in 1957–1958, and immunizations (one or two vaccine injections in 1957–1958 and 1958–1959, and one injection in October, 1959) were coded for computer analysis.

Results

Influenza Attack Rates: Monthly attack rates of febrile illnesses compatible with a clinical diagnosis of influenza are shown in Figure 1 for the three years of observation. For the period beginning in September, 1957, when Asian influenza first appeared, relatively high attack rates (above 14 per 1,000 per month) were maintained throughout, with peaks of 34 and 47 occurring in October, 1957, and February, 1958. The overall case rate for this period was 186 per 1,000. During the following period, September, 1958, through March, 1959, only 21 cases of influenza-like illness were recorded. Such illnesses were rarely observed in workers during the fall of 1959, but in January, 1960, a sharp outbreak occurred, with a peak of 78 cases per 1,000 employees in February. The overall attack rate during the third period was 109 per 1,000 and virtually all cases occurred during an eight-week period from middle January to mid-March.

Asian virus was isolated during the 1957–1958 and the 1960 epidemics, but not during 1958–1959 (Figure 1). Differences were not detected in the strains isolated in 1957–1958 and in 1960. Both groups of viruses had the same growth characteristics in the amniotic sac of the embryonated egg and similar hemagglutination-inhibition titers with fowl and rabbit antisera prepared with the 1957 prototype from New Orleans. A single recovery of influenza B was made during the 1958–1959 season. Other viral agents (particularly parainfluenza) were found in association with clinical respiratory illnesses during the latter period. Beta hemolytic streptococci were not cultured from any of the febrile cases.

Absenteeism as Related to Influenza: Since the influenza syndrome defined in this study represented a severe disabling illness, employee absen-

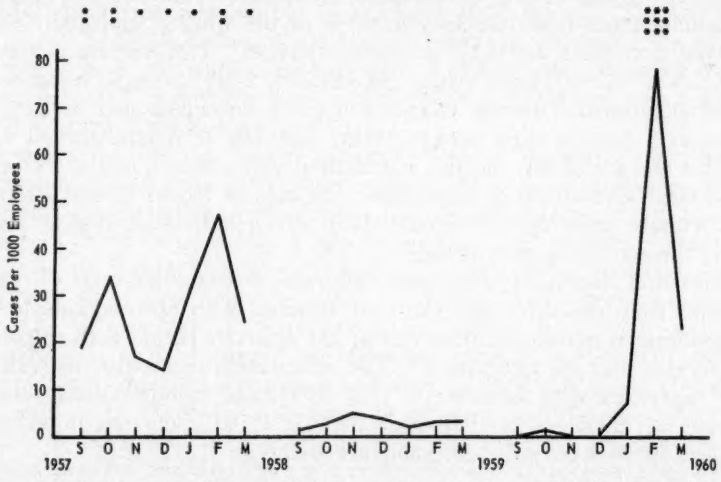

FIG. 1. Monthly attack rates of febrile respiratory disease clinically compatible with influenza, and isolations of influenza A2 in selected cases (*), September–March, 1957–58, 1958–59, and 1959–60.

teeism could be related to the incidence of the disease determined clinically. This was shown by monthly absenteeism rates, expressed as calendar days of absence per 1,000 employees (Figure 2). Absence rates due to all respiratory diseases, as well as to influenza tend to follow the attack rate curves for influenza (Figure 1). The period September, 1957, to March, 1958, was one of high respiratory disease absenteeism with peaks of 210 and 316 days' absence per 1,000 workers attributed to influenza in October and February (Figure 2). Corresponding absenteeism rates for all acute upper respiratory diseases were 386 and 612 days per 1,000 workers for these two months. The September, 1958, to March, 1959, season was one of low absenteeism, with only a slight rise to 147 days per 1,000 employees due to all respiratory illnesses in January. The third period showed a sharp in-

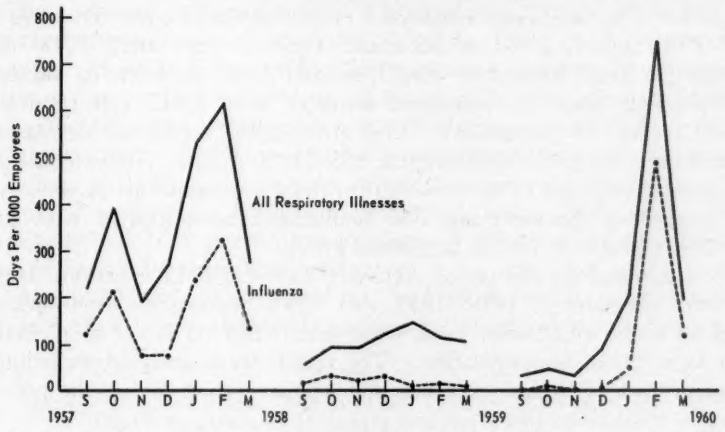

FIG. 2. Disability absenteeism attributed to all upper respiratory illnesses and to influenza, by months, September–March, 1957–58, 1958–59, and 1959–60.

crease that occurred in the winter of 1960, with severe absenteeism rates of 743 (all respiratory illnesses) and 490 (influenza) in February, followed by an abrupt decline in March.

Protective Effect of the Vaccine: The results of vaccine administration to part of the worker population during the period in which each influenza epidemic occurred are shown in Figure 3. The number of illnesses and days of disability attributed to influenza and all time-losing upper respiratory illnesses are shown for 1957–1958 in the posterior plane, and for 1959–1960 in the anterior plane. Cases of clinically diagnosed influenza (shown in the left half of the figure) were reduced from 313 per 1,000 in unvaccinated to 123 in vaccinated employees in the 1957–1958 epidemic; corresponding rates were 114 and 93 in the 1960 outbreak. Disability absenteeism was

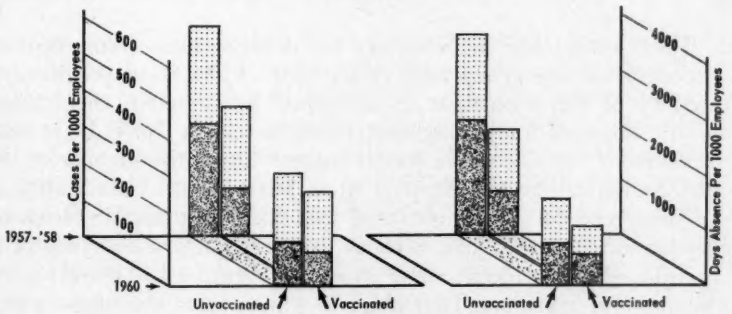

FIG. 3. The effect of influenza vaccine on influenza (lower portion of bars) and other disabling respiratory illnesses (upper portion of bars), manifested by reductions in cases (left half of figure) and absenteeism (right half of figure). Data for the 1957–58 epidemic are shown in the posterior plane, and for the 1960 epidemic in the anterior plane.

also reduced in vaccinated employees (right half of Figure 3). For the 1957–1958 period, 1,000 unvaccinated workers experienced 3,700 days' absence due to all respiratory conditions and 2,140 days due to influenza; corresponding rates for vaccinated workers were 1,940 (all respiratory illnesses) and 750 (influenza). Less striking but significant decreases in absenteeism were recorded during the 1959–1960 season. Rates (expressed as days of absence per 1,000 workers) for the unvaccinated group were 1,490 (all respiratory illnesses) and 730 (influenza), as compared with 1,050 and 530, respectively, for the vaccinated group.

Post-seasonal Evaluation of Antibody Titers of the Population: During the three summers of 1958, 1959, and 1960, hemagglutination-inhibition antibody titers with Asian virus were determined on blood sera obtained from segments of the population. The results were analyzed according to the occurrence of clinical influenza and/or vaccination during the previous

TABLE 1

Influenza Antibody Titers of Serum Pools Prepared with Blood Samples Obtained in July, 1958, and Grouped According to Type and Time of Respiratory Illness During the Preceding Year*

Type of Respiratory Disease	HI Antibody Titers of Serum Pools According to Time of Illness					
	Asian		A-prime/57		B/GL/54	
	July–Dec. '57	Jan.–June '58	July–Dec. '57	Jan.–June '58	July–Dec. '57	Jan.–June '58
None	8	8	4	4	32	32
Coryza, afebrile	11	4	8	4	32	32
Undifferentiated, temperature >101° F.	8	32	6	6	45	45
Pharyngitis	11	16	6	6	32	32
Influenza, ARD, temperature >101° F.	8	32	4	8	45	45

* Blood specimens were obtained from 1,000 employees; each pool contained approximately 40 sera.

year. These studies had as objectives the determination of the degree of past experience of the group with Asian virus, a means of predicting the susceptibility of the population to additional infections in the following season, and the need for prophylactic vaccination. In Table 1 are shown data on antibody titers of serum pools obtained during the summer of 1958. The distribution of the highest pool titers according to classification and time of occurrence of illness indicated that the group had experienced a considerable incidence of Asian influenza between January and June of that year. Although the epidemic curve shown in Figure 1 had shown a lesser incidence in November and December, it is likely that the effect was not observed in pooled sera obtained in July because of fall in antibody titers. No indication of infection by influenza A-prime or B was observed as shown by the uniform titers in all groups.

The results of hemagglutination-inhibition titers of the individual sera with the current influenza strains are shown in Table 2. Evidence of the occurrence of Asian influenza during the preceding season is contained in the greater amount of antibody in the group with a history of influenza in 1958 and 1960. The reduction in antibody to this virus in 1959 could conceivably have been used to predict the possibility of the second epidemic in the winter of 1960. Increases in hemagglutination-inhibition titers with influenza B indicate the presence of this agent during 1958–1959. Levels of antibody in 1960 suggest a low incidence of influenza during 1960–1961 unless influenza A-prime should recur.

Statistical Relationship of Influenza in 1960 to Previous Influenza and/or Vaccination: An analysis was planned to determine statistically the relationship of influenza in 1960 to all previous antigenic exposures to Asian virus, whether by participation in any of the vaccination programs, by actual experience with the disease in 1957–1958, or by any combination of these factors. By means of an electronic computer, a stepwise regression analysis with preset confidence levels demonstrated that only vaccine administered in October, 1959, either alone or in combination with other factors, was associated with significantly reduced likelihood of influenza in 1960.

TABLE 2

Hemagglutination-inhibition Antibody Titers with Current Strains of Influenza Virus in Sera Obtained During the Summers of 1958–59–60 and Grouped According to Vaccination or Illness*

Date of Blood Sampling	Antigen	Mean HI Antibody Titers			Per Cent with HI Titers of <4-4		
		No Vaccine, Not Ill	Vaccinated, Not Ill	Clinical Influenza, Not Vaccinated	No Vaccine, Not Ill	Vaccinated, Not Ill	Clinical Influenza, Not Vaccinated
July 1958 (post-epidemic)	Asian	5.2	8.9	26.9	37.5	25.0	0.0
	A1/57	1.8	—	1.4	80.0	—	80.0
	B/54	13.5	—	22.7	20.0	—	0.0
July 1959	Asian	3.4	10.6	—	62.8	31.1	—
	A1/57	11.2	13.2	—	35.3	27.6	—
	B/54	71.6	135.2	—	0.0	0.0	—
July 1960 (post-epidemic)	Asian	23.6	69.2	41.1	14.6	0.0	11.1
	A1/57	2.6	39.0	2.0	75.0	0.0	77.0
	B/54	95.2	291.9	128.0	0.0	0.0	0.0

* No. of sera tested in 1958—25; 1959—65; 1960—100. Sizes of clinical and vaccinated groups were approximately the same for each year.

A second form of output from the IBM 705 program was a matrix of correlation coefficients showing the relationship of all factors (1957–1958 influenza and/or various vaccine inoculations) to the occurrence of influenza in 1960. There were 36 logically possible factors, alone or in combination, in this relationship. A few of the most meaningful coefficients are shown in Table 3. The relationship between the October, 1959 vaccine and 1960

influenza is expressed by —0.11. The negative sign of the coefficient indicates an inverse relationship; that is, the inoculated individuals had fewer cases of influenza than those who did not receive the vaccine. The value of the coefficient reflects a high level of statistical significance; the probability of achieving such a coefficient from the sample by chance alone is only two in a thousand.

Since the design of the study permitted the extraction of coefficients which express interrelationships between all factors in the analysis, it was possible to relate 1957–1958 vaccine inoculations to influenza occurrence at that time in the first epidemic. This coefficient proved to be identical with that relating October, 1959 vaccine to 1960 influenza, —0.11.

In contrast, none of the other coefficients (relating influenza in 1957–1958, vaccine administered prior to the October, 1959 program, or all combinations thereof to influenza in 1960) indicated a significant reduction in occurrence of influenza. Examples of these correlation coefficients are: 1957–1958 influenza, 0.00; two 1957–1958 vaccine injections, 0.00; two

TABLE 3

Relationship of Asian Influenza in 1960 to Previous Influenza and/or Vaccination

Factor*	Correlation Coefficient†
1	−0.11
2	0.00
3	+0.00
4	+0.01
2, 3, and 4	+0.04

* 1 = Oct. 1959 vaccine. 2 = 1957–58 influenza. 3 = Two 1957–58 vaccine injections. 4 = Two 1958–59 vaccine injections.

† The correlation coefficients indicate the relationship between certain factors and the occurrence of influenza in 1960. Potential range of coefficients: ±1.000 to −1.000. Probability of random occurrence of +0.110 is about 2/1000; coefficients of ±0.04 or less are considered to be statistically insignificant.

1958–1959 vaccine injections, + 0.01; 1957–1958 influenza plus all vaccine injections except October 1959, + 0.04. Values of 0.04 or less are not statistically significant. The sign and value of the coefficients demonstrate that these factors afforded no immunity or protection for Asian influenza in 1960.

DISCUSSION

The serious impact of the two Asian influenza epidemics on this industrial plant can be readily seen when one compares case rates and absenteeism for each of the three years of the study. There could be little doubt that the marked increase in rates in 1957–1958 and 1960 was due to influenza, because the illnesses were clinically compatible with that diagnosis, and virus was isolated in practically all cases selected for study. The contrasting lower rates in 1958–1959 can probably be used as a non-influenza base line for the period since only one influenza B virus was isolated from 158 garglings obtained from cases of respiratory illness.

Although patients observed during the course of the influenza epidemics exhibited a variety of disease patterns, a picture considered characteristic of "clinical influenza" was readily recognized: an illness of abrupt onset with fever, chills, respiratory tract involvement (rhinitis, pharyngitis, bronchitis), and striking constitutional symptoms of headache, muscular aches, and malaise.[2] Such rather typical cases form the basis of the clinical and epidemiologic sections of this report. The pattern of respiratory diseases in refinery workers appeared to follow the illness picture in the community as a whole. The spread of Asian influenza in the fall of 1957 throughout southcentral Louisiana has been previously described,[3-5] and the involvement of school children and their families in the adjacent parish is the subject of a related study.[6]

The value of careful clinical observations in classifying respiratory illnesses has been pointed out,[7] and absenteeism in selected industries has been described as an excellent indicator of the involvement of an adult working population with influenza.[8] In the present study, respiratory syndromes were evaluated by the same physicians, who adhered to fixed criteria throughout the three year study period. Sickness absenteeism of the plant workers was strictly accounted for, and the accuracy of medical department tabulations was checked against payroll figures; consequently, it is felt that consistency of findings and comparability of results have been insured.

Because of the threat of epidemic Asian influenza to workers of an oil refinery and petrochemical plant that must operate continuously, vaccine was offered to employees on a voluntary basis each fall, beginning in 1957. The first year 0.1 to 0.2 ml. monovalent Asian influenza vaccine (200 CCA U/ml.) was administered intradermally. This dose was chosen in order to achieve maximal patient coverage with limited supplies of vaccine. Resultant antibody levels (hemagglutination-inhibition), while generally lower than those achieved with larger vaccine doses subcutaneously, were known to be appreciable;[9,10] the value of such a regimen has since been reported by others.[11-13] The following year, one or two subcutaneous injections of 0.5 ml. polyvalent influenza vaccine were offered, and in October, 1959, a single injection of 0.5 ml. was provided. This was planned as a "booster" in a population with widespread prior antigenic exposure, both to disease and vaccination.

These regimens for the administration of vaccine were not associated with significant disability or morbidity in the worker population. However, limited experience with 1 ml. quantities of commercial polyvalent influenza vaccine injected subcutaneously in wage earners indicated the likelihood of excessive work restrictions from local reactions and disability absenteeism from systemic reactions. These findings are in contradiction to the reports of Boger et al., and Lynch et al., based on studies in populations of an institution and white collar workers, respectively.[14,15] Greene and Beaver, on the other hand, reported significant local reactions in 27.8%

of telephone workers given 1 ml. vaccine subcutaneously; 3.1% of those inoculated lost an average of 2.2 days from work.[16]

Employees vaccinated prior to each epidemic experienced fewer cases of influenza and lower disability absenteeism than unvaccinated workers. In 1957–1958, the influenza attack rate was 313 in unvaccinated and 123 in vaccinated workers, a reduction of 60%. In the 1960 epidemic, the corresponding rates were 114 and 93, a reduction of 20%. Overall absenteeism due to acute respiratory disease was lower in the vaccinated group by 45% in 1957–1958, and by 30% in 1960, while reductions in absences attributed to influenza were 65% and 27%, respectively.

These results may be compared with those reported for the 1957–1958 epidemic in 93,000 telephone company employees by Greene and Beaver.[16] The incidence of "self-diagnosed" influenza was reduced from 296 per 1,000 in non-inoculated employees to 219 in workers who were administered 1 ml. monovalent Asian influenza vaccine. The 7.7% fewer cases were associated with 17.9% reduction in sickness absenteeism, as reported by the employees through a retrospective questionnaire. Gundelfinger et al. reported a 60% reduction in attack rates (58.9 cases per 1,000 per week in unvaccinated, 23.5 cases per 1,000 per week in vaccinated) in recruits who were administered 1 ml. monovalent vaccine at the Great Lakes Naval Training Center during the Asian influenza epidemic of October, 1957.[17] A study of Eastern Airlines personnel at Miami reported a reduction in respiratory absences during periods of the 1957–1958 influenza epidemic following immunization with 0.1 ml. (10 CCA units) of monovalent Asian influenza vaccine.[18] The absence rate was 62 per 1,000 in 2,370 employees receiving one injection of vaccine, as compared with 171 per 1,000 in 1,200 employees receiving no vaccine.

The vaccine dosage administered to refinery workers may be considered suboptimal. Yet, the comparatively small antigenic stimulus of 20 to 80 CCA units of monovalent Asian vaccine administered during the 1957–1958 epidemic was associated with 40 to 60% reduction in clinically recognized cases of influenza and associated absenteeism. A lower though significant degree of protection (20 to 30%) was evidenced by these indices for the February, 1960, epidemic. Here, a single injection, 0.5 ml. of polyvalent vaccine containing 100 CCA units of Asian virus, was administered four months before the outbreak of disease.

These clinical observations suggest that immunity may have been declining four months after vaccine injection. This interpretation is supported by failure of the statistical analysis to demonstrate any evidence of vaccine protection being carried over from one year to the next. There would seem to be need for further study regarding the optimal dose and route, and time of administration of polyvalent influenza vaccine. It is possible that a regimen of two 0.5 ml. doses (250 CCA units each) spaced more widely apart (September and December) might afford equal or better pro-

tection with fewer reactions than the vaccine schedule conventionally recommended. Admittedly, this would not evoke as great an antibody response as a larger total dose, but the peak titers would occur at a time when they were most needed.[18]

The application of results of antibody titers in serum pools prepared by grouping individual sera according to time and type of illness for determination of the major offending agents during the preceding year appears to have some merit. By this procedure blood samples taken at the time of routine physical examinations can be used. In this instance, they were obtained during the summer of 1958 and evidence of Asian influenza during the preceding year was demonstrated by hemagglutination-inhibition titers of the pools. If the population is under continued observation, determination of antibody levels in 25–100 sera arbitrarily selected during the summer appears to be a preferable method of predicting susceptibility of the group. The results described herein should have served to warn against a recurrence of Asian influenza. Similar observations have been made from studies of the epidemiology of influenza as demonstrated by serum pools by Brown et al.[19]

Analysis of the cases of influenza that occurred in 1960 revealed no evidence of immunity due to a previous episode of the disease or to vaccination unless the latter had been administered in the epidemic year. Similar observations were made in Tangipahoa Parish, Louisiana, and in medical personnel in New Orleans.[6] It seems less likely that this will recur a third time, at least in such proportions, since antibody levels appear to be increasing progressively.

Summary

Asian influenza appeared abruptly in personnel of a large petroleum refinery and petrochemical plant in September, 1957, and persisted into the spring of 1958 with peaks in monthly attack rates of 34/1,000 in October, and 47/1,000 in February; the overall rate for the period September, 1957, through March, 1958, was 186/1,000. Then, Asian influenza apparently disappeared in the employee population, remaining absent the following fall and winter, 1958–1959. It recurred in mid-January, 1960, in a sharp, explosive outbreak lasting approximately eight weeks, with a peak monthly rate of 78/1,000 in February and an overall rate of 109/1,000 for the season. Disability absenteeism attributed to influenza closely followed the monthly attack rates, with rates of 200 (October, 1957), 300 (February, 1958), and 500 (February, 1960) days absent per 1,000 workers per month, corresponding to the case incidence peaks. Etiologic confirmation of the respiratory illnesses was obtained by the isolation of antigenically identical strains of Asian virus in both epidemics. Clinical and epidemiologic observations of the appearance and reappearance of Asian influenza in the population were corroborated by isolation of the virus and serologic studies during the three year period.

Vaccination in 1957–1958 and in October, 1959, provided significant levels of protection for inoculated workers during the epidemics. Reduction in cases of clinically recognized influenza in vaccinated employees was 60% in 1957–1958 and 20% in 1960; corresponding reductions in absenteeism were 65% in 1957–1958 and 27% in 1960. Factors of vaccine dosage and schedule which might bring about differences in protection are discussed.

Either individual or pooled serum samplings obtained from the population under observation could be used to determine the virus experience during the previous year or to predict the susceptibility of the group in the approaching season.

Six hundred workers with typical influenza in 1960 were matched with 600 workers free of respiratory diseases during the 1960 epidemic period, and compared with respect to prior antigenic experience with influenza A2, either by having had an influenza illness in 1957–1958, or by vaccination in one or more of the immunization programs from 1957–1960. Only the most recent (October, 1959) vaccination was shown to be effective in preventing influenza in 1960. Other factors, including previous immunization or disease experience, alone or in combination, were found by computer analysis of the data to be without effect upon incidence of the disease in the 1960 epidemic.

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SUMMARIO IN INTERLINGUA

Duo epidemias de influenza asian occurreva inter le membros del personal de un grande petroleria e fabrica petrochimic. Le cifras pro le intensitate del attacco per mense e datos de absentismo a causa maladive ha servite a delinear le curso epidemiologic del morbo: su abrupte declaration in septembre 1957 con persistentia usque al primavera de 1958, sequite per le apparente disparition de illo in le population de obreros e un recurrentia in februario 1960 in le forma de acute e explosive eruption. Le constatationes clinic e epidemiologic esseva corroborate per studios virologic e serologic interprendite in le curso del periodo de tres annos.

Vaccination in 1957 a 1958 e in octobre 1959 provideva nivellos significative de protection pro le obreros inoculate durante le curso del epidemias. Le reduction del incidentia de clinicamente recognoscibile casos de influenza in vaccinate empleatos esseva 60% in 1957 a 1958 e 20% in 1960. Le correspondente reductiones del absentismo esseva 65% in 1957 a 1958 e 27% in 1960. Es discutite le factores del dosage e del programmation del vaccinationes que esseva possibilemente implicate in le causation del differentias de protection.

Specimens de sero tanto individual como etiam collective, obtenite ab le population sub observation, poteva esser usate pro determinar le experientia de invasiones de virus le anno precedente o pro predicer le susceptibilitate del gruppo durante le saison veniente.

Sex centos obreros con casos typic de influenza in 1960 esseva appareate con 600 obreros sin morbo respiratori durante le periodo epidemic de 1960. Esseva trovate que solmente le plus recente vaccination—illo de octobre 1959—esseva efficace in prevenir influenza in 1960. Altere factores, incluse previe immunisationes e previe

contractiones del morbo, habeva nulle influentia super le occurrentia del morbo in le epidemia de 1960.

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PERCUTANEOUS TRANSHEPATIC CHOLANGIOGRAPHY *

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Introduction

The task of differentiating obstructive jaundice from hepatocellular jaundice is frequently exceedingly difficult. It is recognized that viral hepatitis may masquerade as obstructive jaundice in laboratory tests, and it is equally appreciated that obstructive jaundice may give evidence of hepatocellular damage, particularly if it has been of long standing. To complicate the problem further, the entity of intrahepatic cholestasis must be appreciated when a surgical approach to the obstructed state is considered. Within the past several years, a number of papers have appeared that outlined the technic of injecting dye directly into the biliary tree in states of obstructive jaundice, by a percutaneous transhepatic approach.[1-10]

The development of this procedure has been reviewed [11] in a recent paper in which eight cases were reported. Because of our initial encouraging results we have continued to explore the efficacy of this procedure and, where indicated, to modify our technic to increase its safety and effectiveness. Kidd [3] has listed the indications for this procedure: (1) to investigate the cause of biliary symptoms after cholecystectomy; (2) to diagnose the presence and site of carcinoma affecting the biliary system; (3) to demonstrate the presence, location, and number of calculi in the bile ducts; (4) to measure pressure of bile in the biliary system when spasm of the sphincter of Oddi is suspected, and to investigate the use of antispasmodic drugs; (5) to diagnose the presence of obstructive jaundice as opposed to nonobstructive jaundice. Remolar et al.[4] have added two further indications: (1) the introduction of a polyethylene tube into the biliary tree for the injection of antibiotics; (2) the creation of an external biliary fistula without an open operative procedure.

We would like to add one more indication which we feel to be an extremely important use of this technic: the elucidation of the status of the biliary tree in cases of congenital biliary atresia. It is well known that in

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the large majority of these cases the biliary tree is so maldeveloped that operative intervention would be of no benefit. Nevertheless, in some of these cases the biliary tree is sufficiently developed for an operation to assist in promoting biliary drainage into the gastrointestinal tract.

Our experience has been limited to two such cases, both of which were diagnosed as having congenital biliary atresia. Both of these infants had had a transhepatic cholangiogram done under general anesthesia. The first case did not have congenital biliary atresia at all, but had a giant cell hepatitis. This was diagnosed correctly preoperatively after a percutaneous transhepatic cholangiogram had demonstrated the absence of a distended biliary tree. The procedure was followed immediately by a definitive liver biopsy. Since we had satisfied ourselves that there were no large bile ducts to be entered and therefore no chance of creating a bile (chemical) peritonitis, we did not hesitate to perform this procedure. The second case proved to be a true case of congenital biliary atresia. Numerous minute bile ducts were demonstrated by this technic, but no major duct could be found that would have been useful for an anastomosis. We were unwilling to rely completely upon these findings and operated in the conventional manner. Unfortunately, this surgery only served to confirm the impression obtained by the use of the transhepatic cholangiogram.

Method

The patient's coagulation mechanism is checked to be certain that there is no bleeding tendency. No oral intake is allowed for at least four hours prior to the procedure. Immediately before the procedure, the patient is given an intramuscular injection of meperidine, 75 mg., and sodium phenobarbital, 60 mg. The patient is positioned on the x-ray table, after which the lower edge of the liver is marked with an antiseptic solution, and the area chosen for initial injection is infiltrated with 2% Xylocaine. The site usually chosen is in the mid-clavicular line immediately beneath the right costal margin. Local anesthetic is injected through all layers of the abdominal wall and into the capsule of the liver. A small incision is made to facilitate the passage of the needle. A six-inch long, 18 gauge, thin-walled spinal needle with stylet is introduced through the opening into the liver. The direction of introduction is posteriorly and superiorly at an angle of 45 degrees and parallel to the mid-line. The needle is introduced to approximately four inches in depth. The stylet is then removed and a plastic interconnecting tube is attached between the needle and a 50 ml. syringe. An assistant then applies gentle, continuous suction with the syringe while the operator very slowly and uninterruptedly withdraws the needle from its point of maximal penetration. The patient is allowed to breathe normally during this procedure. The withdrawal of the needle is usually done at the end of expiration when there is a momentary pause in respiratory motion.

When bile is aspirated, the further withdrawal of the needle is stopped

and as much material as possible is removed. When no more bile can easily be aspirated, 20 ml. of 70% Urokon Sodium is introduced through the polyethylene tube into the bile radicle. An x-ray taken at this time is studied to determine whether additional films are to be taken. At the termination of the procedure as much dye and bile as possible are again aspirated from the biliary tree. The procedure can either be terminated at this point by removing the needle, or, if indicated, a No. 50 polyethylene tube can be introduced through the needle into the bile radicle, after which the needle may be removed. The bile initially aspirated then undergoes culture and cytologic examination.

On several occasions we have entered a radicle of the biliary tree too small to allow enough bile to be removed for satisfactory decompression of the biliary tree. In these cases we introduced the contrast material, and at the termination of the procedure made a second percutaneous needle puncture. This was accomplished in an area where the previous films had identified the main bile ducts, thereby increasing our chances for adequate decompression of the biliary tree through this second puncture site.

It has been our experience that a bile radicle is not always entered during the first passage of the needle, and we have arbitrarily limited ourselves to four insertions into the liver. We make one attempt in each of four quadrants, and if no bile radicle is entered we conclude that unsatisfactory dilatation of the biliary tree makes the procedure impractical.

Often, a blood vessel is entered and blood is aspirated into the syringe. At these times we continue to withdraw the needle until no more blood is aspirated, then we disconnect our tubing to flush out the system with sterile saline. We reinsert the stylet into the needle to make certain that no clotted blood has obstructed the lumen, then we reconnect the tubing to proceed with needle withdrawal and aspiration.

Where a biliary radicle cannot be entered during any of the four insertions through the liver, a liver biopsy is done immediately, using the standard accepted technics. There is no fear of creating a biliary fistula or bile peritonitis in the absence of evidence of dilated biliary radicles.

Results

Forty procedures were carried out between May, 1958, and August, 1960 (Table 1). The biliary tree was demonstrated in 30 cases, while in 10 a biliary radicle could not be located for injection. Subsequent studies in these 10 cases revealed eight to have had hepatocellular jaundice. Since two patients had jaundice due to obstruction of the biliary tree, these cases must be considered a failure of the procedure. The proper origin of the jaundice then was established in 38 cases, whereas the correct diagnosis was missed in two. Of the 30 cases in which the biliary tree was demonstrated, in eight jaundice was due to stones in the common duct, in three to postoperative stricture, and in one to primary biliary atresia. In 18 cases jaundice was

due to carcinoma of either the ampulla of Vater or the pancreas, or to primary carcinoma of the biliary tree.

No mortality was directly related to the procedure and the overall morbidity has been low. In 28 patients there has been no discomfort whatsoever. In eight patients there was right upper quadrant pain immediately following the withdrawal of the needle. This was transient in nature and required only a single injection of meperidine, 100 mg., for relief. Four patients developed marked right upper quadrant pain and concommitant signs of peritoneal irritation upon withdrawal of the needle. These were operated upon immediately, and in each case a small collection of bile was found localized at the puncture site with surrounding peritoneal reaction. No cases of generalized chemical peritonitis were encountered. Since the

TABLE 1

Analysis of Results of Transhepatic Cholangiography

Total Number of Procedures—40

Correct Diagnosis *Established* by Transhepatic Cholangiography	38	Correct Diagnosis *Missed* by Transhepatic Cholangiography	2
Biliary radicle entered	30		
Congenital biliary atresia	1		
Postsurgical duct stricture	3		
Choledocholithiasis	8		
Carcinoma of pancreas Common duct Ampulla of Vater	18		
Biliary radicle not entered	10		
Hepatocellular jaundice	8		
	2	Obstructive jaundice	

Total Number of Complications—12

No Complications	Transient Pain (Necessitating One Injection of Meperidine)	Bile Peritonitis (Necessitating Immediate Surgery)	Mortality
28	8	4	0

large majority of our patients experienced little or no discomfort from the procedure, we have not restricted the use of the study only to the period immediately preceding surgery. Since the possibility of a confined bile peritonitis does exist, however, immediate surgery is always available if it is needed. In all of the cases in which elective surgery was performed (one to 12 days following transhepatic cholangiogram) no evidence of bile leakage or bleeding from the puncture site in the liver was observed.

DISCUSSION

There can be no denying the value of a procedure that correctly differentiates between hepatocellular jaundice and obstructive jaundice, while providing hepatic tissue for microscopic diagnosis in the event of hepato-

cellular disease, and which gives a cholangiogram demonstrating the site of obstruction in obstructive jaundice. The percutaneous transhepatic cholangiogram is such a procedure. Granting the diagnostic value of this procedure, it then becomes mandatory to determine its safety. The two obvious hazards would be those of massive bleeding from the liver puncture site, and the creation of a biliary fistula with chemical peritonitis, resulting from decompression of the distended biliary tree into the free peritoneal cavity. Careful attention to the integrity of the coagulating mechanism prior to the procedure makes the danger of bleeding no greater than that from a routine liver biopsy, and perhaps even less, because the caliber of the needle is considerably smaller. We have had no bleeding problems, and in searching the literature we found only one reported case of intra-abdominal hemorrhage.[2] No coagulation studies had been carried out in this particular case. The more serious of the two problems appears to be that of chemical peritonitis caused by a distended biliary radicle forcing bile into the peritoneal cavity. We encountered four instances of major bile leaks that necessitated immediate surgical intervention. All four survived the surgery and since each was obviously due to biliary tract obstruction and required surgical intervention anyway, this complication served only to hasten the inevitable operation. Consequently, arrangements for immediate surgical intervention are always available when this procedure is to be done.

In a review of the literature, Richieri [13] reports that in 65 cases, 30 developed some degree of bile peritonitis and 16 died as a result of this complication. On the other hand, Garcia [12] reported two cases of bile peritonitis in 150 punctures with no mortality. Housset and Vantsis [7] report a complication rate from bile peritonitis of 10%, which is the same as we found.

The part of the technic that markedly reduces the possibility of a bile peritonitis is that of decompressing the biliary tree by aspirating as much bile as possible initially, and again as much bile and dye as possible following the procedure. In our more recent cases when we have felt that we have not adequately decompressed the biliary tree, we have made a second puncture in an area where we knew, by our previous x-rays, that the main ducts were located. We have not considered the procedure terminated until adequate decompression has been achieved. In these latter cases we have observed no bile peritonitis.

Prior to the advent of this procedure, the need for prolonged observation of a patient in whom the differential diagnosis between obstructive jaundice and hepatocellular jaundice was not clear had been widely accepted. This is imposed by the high morbidity and mortality of a surgical exploration on the patient with an active hepatocellular process. The technic of transhepatic cholangiography eliminates this otherwise long observation process by allowing a differentiation to be made immediately. If a bile radicle is entered and a cholangiogram obtained, the point of obstruction and fre-

quently the etiology of the obstruction are readily apparent. If, following a careful probing of the liver, no distended ducts are encountered, it is considered safe to proceed with a liver biopsy and establishment of a hepatocellular basis for the jaundice. In either case, correct therapy can then be instituted immediately, eliminating a long period of waiting.

An interesting facet that has become apparent from this procedure is that patients manifesting severe pruritus have obtained almost immediate relief when the biliary tree is decompressed. We have noticed dramatic relief of pruritus when as little as 25 to 30 ml. of bile has been aspirated from the biliary tree. Fuentes et al.[6] have also made this same observation.

Regarding the second indication of Remolar et al.,[4] we placed a polyethylene tube into the biliary tree of a patient who was considered to have an inoperable carcinoma of the pancreas. Our initial aspiration of the biliary tree through the spinal needle produced 35 ml. of a clear, colorless bile. After we inserted the polyethylene tube, an additional 150 ml. of golden bile was excreted over a 48-hour period, before the tube was inadvertently dislodged from the biliary tree.

The use of a flexible polyethylene tube between the aspirating syringe and the exploring needle is considered to be a vital safety measure. This tube markedly reduces the chances of lacerating the liver, since a rigid system is not created. Rather, the patient is allowed to breathe normally and the needle is allowed to move with respiratory motion. The needle is touched for withdrawal only at the end of a respiratory cycle, when the diaphragm is momentarily still. We have found that this technic obviates the need of immobilizing the right leaf of the diaphragm by injection of the phrenic nerve as advocated by Fuentes et al.[6]

Because of the great diagnostic value of this test and because of its proved low mortality and morbidity when correctly done, this procedure has been gaining markedly in its popularity, particularly in the Latin-American countries. Garcia[12] reports 150 punctures. Wilkes et al.[10] report 41 procedures, in which a proper diagnosis was made in 40. Thirty-eight were obstructive in nature, two were hepatocellular, and one was a missed diagnosis. Fuentes et al.[6] report 31 cases in which 19 were due to obstructive jaundice, with successful cholangiograms being obtained, and 12 in which the jaundice was correctly diagnosed as being due to hepatocellular disease. There were no missed diagnoses in this series. In 1956, Royer et al.[5] reported 19, 15 showing successful cholangiograms and four due to hepatocellular disease. Felci[8] reports seven cases, all of them due to obstructive jaundice and all correctly diagnosed.

It would seem obvious from this growing list of successfully diagnosed cases that the procedure of percutaneous transhepatic cholangiography has a real place in our diagnostic armamentarium. As we gain more experience and evolve additional safety measures we will further reduce the already low mortality and morbidity rate.

Summary

1. Percutaneous transhepatic cholangiography is a procedure which can correctly differentiate between obstructive jaundice and hepatocellular jaundice when a clear cut diagnosis is not otherwise apparent. If the jaundice is obstructive in origin, the cholangiogram will show the point of obstruction and frequently the etiology of the obstruction. If the jaundice is hepatocellular, a liver biopsy may be safely obtained.

2. The authors' experience in 40 procedures is presented. In 30 obstructive jaundice was present and correctly diagnosed; in eight hepatocellular jaundice was present and correctly diagnosed; in two obstructive jaundice was present and missed by the procedure.

3. No mortality was encountered with the procedure.

4. The morbidity was low. In 28 patients there was no discomfort; in eight patients there was transient right upper quadrant pain that responded to analgesics; in four patients localized bile peritonitis developed. These patients were sent to immediate surgery and all survived the operation.

5. The technic of the procedure is reviewed.

6. Six case histories and x-ray findings are presented, demonstrating a variety of conditions found.

7. A review of the world literature is presented, emphasizing the value and safety of the proceure.

Appendix

Case Reports

Case 1. A 68-year-old white female was admitted to the hospital because of nausea, vomiting, and weakness of two to three weeks' duration, and jaundice, dark urine, and normal colored stool of one week's duration. There was an associated six pound weight loss. There was no history of pain, no exposure to jaundiced individuals, injections, transfusions, or icterogenic drugs.

Physical examination revealed generalized icterus. The liver edge was palpable two to three fingerbreadths beneath the right costal margin. It was nontender and the edge was sharp.

Laboratory data revealed a bilirubin of 33 mg.%; cephalin-cholesterol flocculation, 1-plus; alkaline phosphatase, 14 Bodansky units; serum glutamic oxalopyruvic transaminase, 91 U; and urine urobilinogen, positive in trace amounts.

A transhepatic cholangiogram was done (Figure 1) which revealed a stone impacted in the distal portion of the common bile duct. Three days later, a choledochostomy was performed and the stone was removed. The postoperative course was uneventful.

Case 2. A 26-year-old Negro female was admitted to the hospital because of right subcostal pain, nausea, and vomiting of 24 hours' duration, and obvious jaundice. The patient had had a similar attack four years before and was also jaundiced at that time. She was treated conservatively at that time and the pain and jaundice disappeared without specific therapy. Four months prior to this episode, she had been hospitalized for a supracondylar fracture of the left humerus, at which time she was found to have a hemoglobin of 7 gm.%, and sickle cell disease was diagnosed. She was given two units of whole blood. Her history revealed a minimal to moderate

alcohol intake. There was no known exposure to icterogenic drugs or hepatotoxins, and no contact with jaundiced individuals.

Physical examination revealed a thin, normally developed, icteric Negro female, with a liver that was palpable 5 cm. below the right costal margin and tender. The spleen was not palpable.

Laboratory data revealed a hemoglobin of 7.6 gm.%; bilirubin, 4.9 mg.%, direct; 27.1 mg.%, indirect; alkaline phosphatase, 12.2 Bodansky units; thymol turbidity, 0.5 U; cholesterol, 447 mg.%, total; SGO-T, 530 U.

Flat plate of the abdomen revealed numerous radio-opaque calculi in the region of the gall-bladder. The differential diagnoses therefore included obstructive jaundice due to cholelithiasis and choledocholithiasis, hemolytic jaundice, and homologous serum hepatitis.

The patient remained afebrile. Her bilirubin steadily increased to a total of 72 mg.%. Her nausea, vomiting, and right upper quadrant pain persisted. An upper

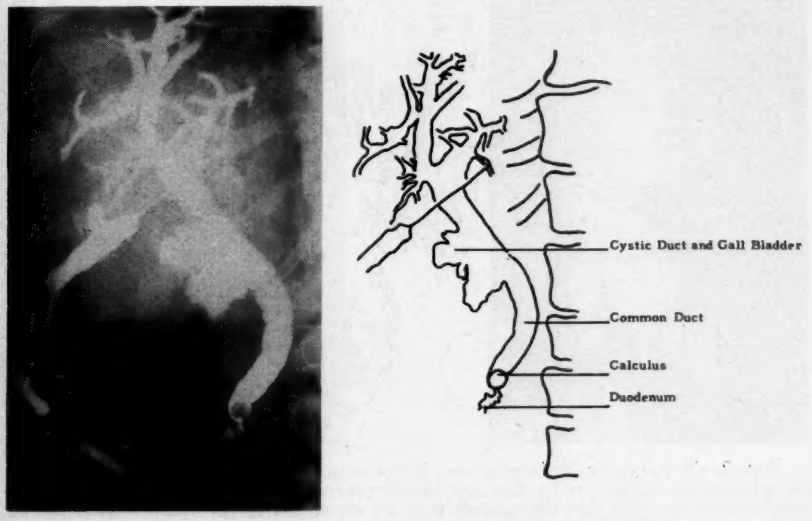

FIG. 1. Transhepatic cholangiogram. There is dilatation of the intra- and extrahepatic biliary tree. The cystic duct is seen to be markedly dilated. The gall-bladder is beginning to fill. The common duct is uniformly dilated and in its most distal portion a radiolucency representing the calculus is noted. A small amount of dye is noted to leave the common duct and enter the duodenum.

gastrointestinal series was negative. A surgical consultant was reluctant to do an exploratory procedure because of the possibility of this being an active serum hepatitis.

A transhepatic cholangiogram was performed (Figure 2). It demonstrated a markedly dilated intrahepatic as well as extrahepatic biliary tree, and a distended gall-bladder containing numerous calculi. The distal portion of the common duct was dilated and there was a smooth termination in the region of the ampulla of Vater. No dye was seen to enter the duodenum.

The following day a cholecystectomy and choledochostomy was performed, with removal of stones. A liver biopsy revealed no evidence of acute hepatitis. The patient had a benign postoperative course with gradual resolution of her jaundice.

Case 3. A 72-year-old Negro female was admitted to the hospital in December, 1959, because of painless jaundice of one month's duration. She had been seen in the neurology clinic one month prior to admission because of left-sided weakness and numbness, and a diagnosis of right cerebral artery thrombosis was made. She was placed on ambulatory anticoagulation, using Dicumarol, which was discontinued in late November because of progressively prolonged prothrombin times. During the period of anticoagulation the patient's prothrombin time was measured weekly. When this medication was discontinued, the patient began to complain of anorexia, nausea, and occasional vomiting, but no pain or pruritus. There was no previous history of jaundice, no exposure to hepatotoxins, icterogenic drugs, or jaundiced individuals.

Physical examination revealed an elderly Negro female with a left hemiparesis and obvious jaundice. There was no hepatosplenomegaly. The stool was of a yellow brown color.

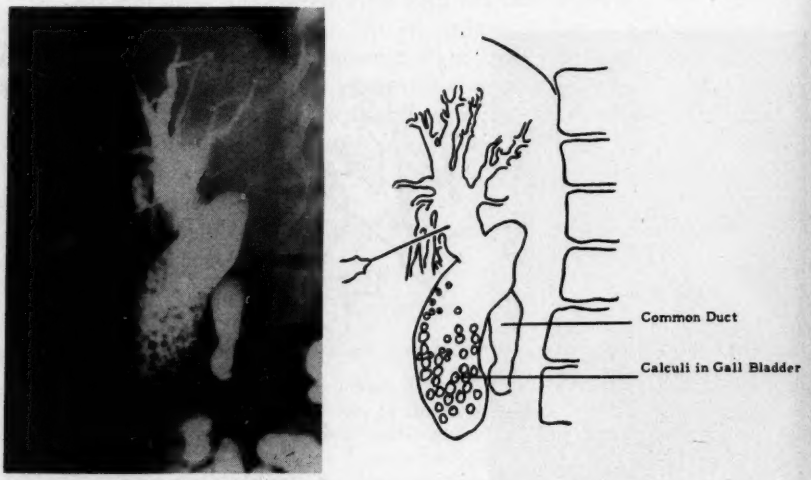

FIG. 2. Transhepatic cholangiogram. There is marked dilatation of both the intra- and extrahepatic biliary tree. The gall-bladder is markedly dilated and is filled with numerous calculi. The dye stops abruptly at the distal end of the common duct, and no dye is seen to enter the duodenum.

Laboratory data revealed a hemoglobin of 9.2 gm.%; bilirubin, 8.1 mg.%, direct, and 17.1 mg.%, total; thymol turbidity, 0.5 U; alkaline phosphatase, 14 Bodansky units; cholesterol, 345 mg.%; SGO-T, 176 U. An upper gastrointestinal series and barium enema were negative. Prothrombin time was normal.

A transhepatic cholangiogram was done (Figure 3) three weeks following admission because of the persistent abnormalities in the laboratory findings. These revealed a markedly dilated intra- and extrahepatic biliary tree with a dilated cystic duct and a distended gall-bladder. The distal end of the common duct revealed a smooth tapering termination, with no dye entering the duodenum during the examination.

The patient was scheduled for surgery, with preoperative diagnoses of carcinoma of the pancreas and obstruction of the intrahepatic portion of the common duct. Before surgery could be performed, however, she had an episode of emesis and massive aspiration of vomitus, and died 11 days following this episode, of staphylococcic pneumonitis. A post-mortem examination revealed carcinoma of the

head of the pancreas, and complete obstruction of the intrahepatic portion of the common duct.

Case 4. An 84-year-old white male was admitted to the hospital because of progressive jaundice of five weeks' duration. There was no pain associated with the jaundice but there was marked pruritus that increased progressively, and a 40 pound weight loss over an 18-month period. There was no history of exposure to jaundiced individuals, hepatotoxic or icterogenic drugs, or injections.

Physical examination revealed a deeply jaundiced male with signs of obvious weight loss. The skin was covered with numerous excoriations due to scratching. The liver was enlarged two inches beneath the right costal margin and was not tender. The stool was a light tan color and was negative for occult blood.

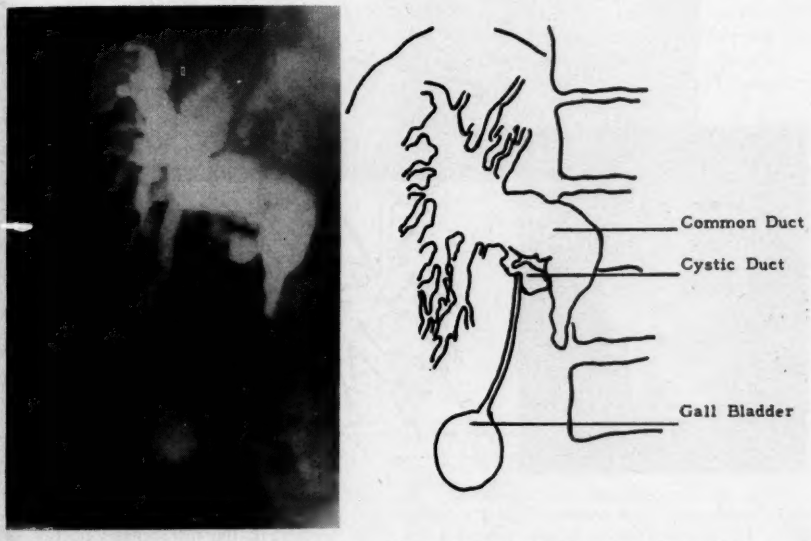

FIG. 3. Transhepatic cholangiogram. There is marked dilatation of the intra- and extrahepatic biliary tree. The cystic duct is markedly dilated and dye is beginning to fill the gall-bladder. The distal half of the common duct is uniformly narrowed and no dye enters the duodenum. This narrowed portion of the common duct corresponds to the area that is surrounded by the carcinomatous pancreas.

Laboratory data showed a hemoglobin of 14.8 gm.%; bilirubin, 26.1 mg.%, direct, and 47.6 mg.%, total; alkaline phosphatase, 19.5 Bodansky units; cholesterol, 432 mg.%; SGO-T, 168 U.

One week following admission, a transhepatic cholangiogram was done (Figure 4) and the right intrahepatic duct was found to be markedly dilated. The dye did not progress further than the main portion of the right hepatic duct. In the region where it should normally join the left intrahepatic duct there was a smooth conical termination of the radicle. Three days later, the patient was operated upon and the extrahepatic biliary tree was found to be collapsed. Acute and chronic cholecystitis was found. A small nonobstructing polyp was seen in the region of the porta hepatis. At the junction of the right and left hepatic ducts a tumefaction was found, which was revealed to be an adenocarcinoma by microscopic examination. An attempt was made to force a catheter through the obstruction. The patient tolerated the surgery poorly, and on the following day he developed a high fever, went

into shock, and died. Blood cultures taken immediately ante-mortem revealed an *Escherichia coli* septicemia. An autopsy was not performed.

Case 5. A 69-year-old white female was admitted to the hospital with jaundice of six weeks' duration. Eight months earlier, the patient had had an attack of right upper quadrant pain, anorexia, nausea, and vomiting, and was admitted to another hospital for studies.

An oral cholecystogram showed no filling of the gall-bladder. The patient then had a cholecystectomy which revealed cholecystitis, but no cholelithiasis. The common duct was not explored at that time. Two weeks following this surgery, the patient again had right upper quadrant pain and anorexia, and was found to be jaundiced. An intravenous cholangiogram was done during the fourth postoperative week, and showed no filling of the common bile duct. This was attributed to the high serum bilirubin. The pain gradually subsided, the jaundice slowly diminished, and the patient was discharged from the hospital.

At the time of this present admission physical examination revealed generalized icterus. There was bilateral xanthelasma. The liver was palpable two inches be-

FIG. 4. Transhepatic cholangiogram. The needle is entering a small radicle of the right intrahepatic duct system. The dye outlines the intrahepatic portion of the right hepatic duct. No dye is seen to progress beyond the distal portion of the intrahepatic portion of the right hepatic duct. Carcinoma obstructing the duct at this point was found at subsequent surgery.

neath the right costal margin and was moderately tender. The stools were brown in color.

Laboratory data revealed a hemoglobin of 13 gm.%; bilirubin, 6.3 mg.%, direct, and 10.3 mg.%, total; cephalin cholesterol flocculation, negative; alkaline phosphatase, 27.2 Bodansky units; cholesterol, 474 mg.%; SGO-T, 102 U; urine urobilinogen, positive, 1:300; prothrombin time, normal.

Two weeks following admission, because of failure of the bilirubin to decrease, a transhepatic cholangiogram was done (Figure 5). It revealed moderate dilatation of the intra- and extrahepatic biliary tree. The cystic duct stump was seen to be dilated. Approximately one inch distal to the cystic duct, the common duct became markedly narrowed for the remainder of its length. Dye was seen to pass into the duodenum, flowing both proximally and distally into the stomach and into the third portion of the duodenum. The pancreatic duct was also filled in a retrograde fashion. Three days following the transhepatic cholangiogram, the patient was operated upon and a primary carcinoma of the common duct was found, with obvious carcinomatous spread to the liver.

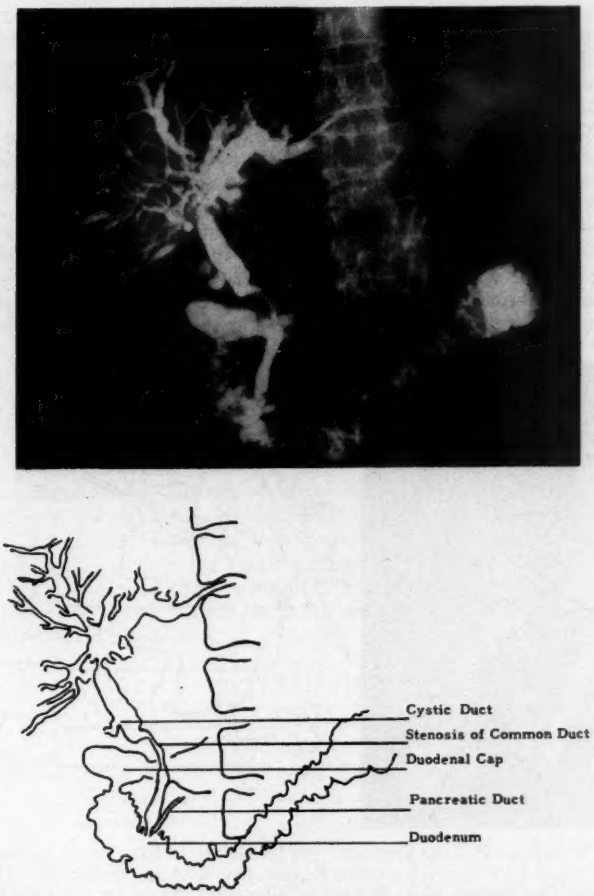

FIG. 5. Transhepatic cholangiogram. There is only slight dilatation of the intrahepatic portion of the biliary tree and of the common hepatic duct. The cystic duct stump is seen to be dilated, and distal to this point the common duct is seen to be markedly stenotic. The most distal portion of the common duct is seen to be normal in caliber and there is a reflux of dye into the pancreatic duct as well as into the duodenum. Subsequent surgery showed a primary ductal carcinoma to be involving this segment of the common duct.

Case 6. A 47-year-old white female was admitted to the hospital because of jaundice, shaking chills, spiking fever, and right upper quadrant pain of two weeks' duration. Three years previously the patient had had a cholecystectomy for cholelithiasis and at that time the common duct was inadvertently ligated. This was recognized during surgery and the stricture was repaired. A T tube was left in place for six months. Following the removal of the T tube, the patient had numerous recurrent attacks of cholangitis, and two years later an attempt at common duct repair was made. The patient again had prolonged T tube drainage during which time she was asymptomatic, and following the removal of the T tube she again had repeated attacks of cholangitis. Each attack was accompanied by some degree of jaundice.

At the time of the present admission, physical examination revealed obvious jaundice, a low grade fever ranging from 100 to 102° F., and numerous spider angiomata over the upper thorax. The liver was palpated three fingerbreadths beneath the right costal margin and was tender. The spleen was palpated two fingerbreadths beneath the left costal margin and was not tender.

Laboratory data revealed a total bilirubin of 7.1 mg.%; cephalin cholesterol flocculation, negative; thymol turbidity, 3.5 U; alkaline phosphatase, 26.8 Bodansky units; cholesterol, 392 mg.%; SGO-T, 78 U. A splenoportogram revealed a splenic pulp pressure of 260 ml. of water. The splenic and portal veins were dilated, and showed numerous collateral channels forming gastric and esophageal varices.

A transhepatic cholangiogram was done (Figure 6) and it revealed a dilated intrahepatic biliary tree in the region of the porta hepatis.

The common hepatic duct was markedly stenotic for a distance of approximately one and one-half inches, distal to which the common duct then assumed normal

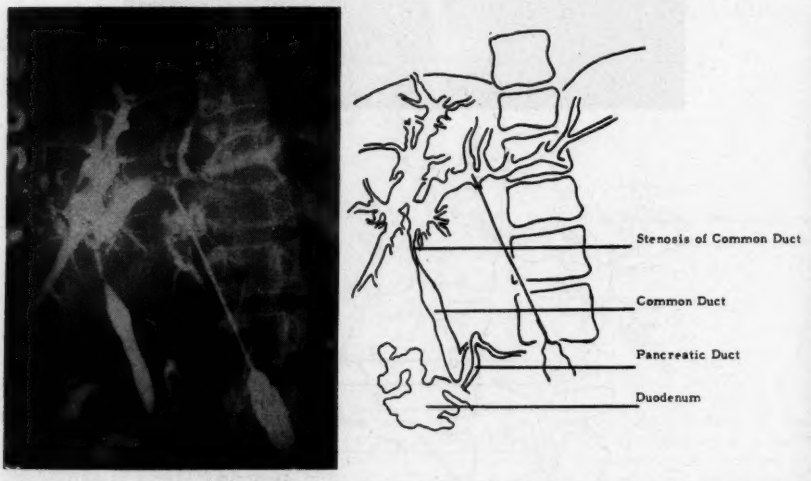

FIG. 6. Transhepatic cholangiogram. The intrahepatic biliary tree is moderately dilated. The most proximal portion of the common hepatic duct is markedly stenotic. The remainder of the common duct appears to be of normal caliber and dye passes from the common duct into the duodenum and in retrograde fashion into the pancreatic duct. This area was found at surgery to be densely fibrotic and unsuitable for surgical repair.

caliber. Dye was seen to flow into the duodenum and also retrograde into the pancreatic ducts.

Three days following the transhepatic cholangiogram, the patient had surgery in an effort to correct the stenosis in the region of the porta hepatis, but because of the dense scar tissue, it could not be done. The left lobe of the liver was incised; a bile duct was identified, and a loop of the jejunum was brought up to the liver in an attempt to create a biliary jejunal fistula. The patient had an uneventful postoperative course, and at the time of the last follow-up, was anicteric and had no further attacks of cholangitis.

ACKNOWLEDGMENTS

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to us; to Doctors Lieberman, Parks, and Widrich, and their respective Departments of Radiology, for their cooperation in carrying out the technical aspect of the studies; to Dr. O. Lopez, for his excellent translations of the foreign literature; and to Miss Sheila Presser, for her technical assistance in the preparation of the paper.

SUMMARIO IN INTERLINGUA

Pro differentiar inter jalnessa obstructive e jalnessa hepatocellular—un objectivo que non es attingibile per medio del constatationes clinic e laboratorial de routine—le technica de percutanee cholangiographia transhepatic in combination con biopsia hepatic a agulia ha essite utilisate. Le methodo esseva usate in 40 occasiones, resultante in le establimento del correcte diagnose in 38 casos. Le serie includeva solmente duo casos in que le diagnose esseva perdite. In le serie de 38 patientes pro qui le correcte diagnose esseva trovate, penetration de un radicula biliari esseva effectuate 30 vices, e roentgenogrammas determinava alora le sito del obstruction. In 10 casos il non habeva penetration de un radicula biliari, e octo de illos esseva recognoscite como de origine hepatocellular, con verification per biopsia hepatic a agulia. In duo del dece casos, penetration de un radicula biliari non esseva effectuate, le biopsia hepatic a agulia non monstrava vitiation hepatocellular, e le subsequente intervention chirurgic demonstrava jalnessa obstructive que habeva escappate al detection per le duo mentionate technicas. Ex le total de 40 interventiones, 28 esseva completate sin complication. Dolores transiente necessitava un injection de meperidina in octo casos, e in quatro un localisate peritonitis biliari se disveloppava e requireva un operation immediate pro obtener le decompression del arbore biliari. Omne le patientes superviveva. Es opinate que con le appropriate grado de circumspection e con le effectuation del operation secundo le hic presentate instructiones, le procedimento es salve e merita esser includite in nostre armamentario diagnostic in le diagnose differential de jalnessa.

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THE DIAGNOSTIC VALUE OF LYMPHANGIOGRAPHY *

By Laird Jackson, M.D., Sidney Wallace, M.D.,† Burton Schaffer, M.D., John Gould, M.D., Simon Kramer, M.D., and Arthur J. Weiss, M.D., *Philadelphia, Pennsylvania*

Lymphangiography, the radiographic demonstration of the lymphatic system by intralymphatic injection of contrast material, has, in our experience, proved to be a new and useful diagnostic tool. Early attempts to visualize the lymphatic system radiographically consisted of either injecting the contrast material into subcutaneous tissues for uptake into adjacent lymphatics,[1] or direct injection into large palpable peripheral lymph nodes.[2-4] Kinmonth, in 1955, devised a practical method for direct intralymphatic injection of the contrast material to study lymphedema of the leg.[5-9] We have modified this method to gain two important advantages: (1) by slow bilateral injection of the lower extremities we are able to visualize an important area which was not shown by previous technic—the retroperitoneal nodes; (2) through the use of an oil contrast medium we can more clearly delineate the architecture of the individual lymph nodes and retain visualization for several weeks. We have now studied 140 patients by this method. The clinical application of this procedure is presented here.

Method

The technic of lymphangiography is described in detail in a previous publication by the present authors.[10] Briefly, it consists of the initial injection of 0.5 ml. of a mixture containing equal parts of 0.5% Evans Blue Dye and 1% procaine hydrochloride into the intradermal tissue of the interdigital web space between the first and second digits of the extremity. The procaine minimizes the pain of injection, and the blue dye is selectively absorbed by the lymphatics, making them identifiable in 15 to 30 minutes. At this time, using aseptic technic, a small skin incision is made proximal to the injection site and a lymphatic conveying the blue dye is identified, isolated, and cannulated with a short 25 to 30 guage needle, which is secured in place by a ligature. The needle is previously fitted to a polyethylene tube which is in turn connected by an adapter to a 10 ml. syringe. Ethiodol, an ethyl ester of poppy-seed oil containing 37% iodine, is injected from the syringe by applying low and constant pressure by means of a manually

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operated apparatus. The contrast material is forced into the lymphatic system at a rate of approximately 7 ml. per hour. Undue pressure may cause extravasation of the contrast material outside of the lymphatics into the extremity. Approximately 10 ml. of the contrast material are injected into the lower extremity or 5 ml. into the upper extremity. Roentgenograms are then taken of the appropriate areas at the completion of injection, and again 24 hours later.

Results

Lymphatics: With injection of a single lymphatic in each foot, the lymphatics of the leg and the lymphatics and lymph nodes of the inguinal, external, and common iliac (Figure 1A) and para-aortic areas (Figure 1B, C) are visualized, as well as the thoracic duct (Figure 1D) and the supraclavicular nodes. Injection of a lymphatic in the hand visualizes the lymphatics of the arm, as well as the lymphatics and lymph nodes of the axillary and supraclavicular areas. The lymphatics will remain visualized for less than an hour in the normal individual and can be studied in the initial roentgenograms. The contrast material will clear from all lymphatics within 24 hours, so that the nodal architecture is best studied in the 24-hour roentgenograms. The normal node will retain the contrast material for from four to six weeks and the abnormal node will usually retain it for a longer period.

Normal lymphatics are fine in caliber and the single injected lymphatic parallels the venous flow through the distal extremity towards the axillary or inguinal lymph nodes. The lymphatics generally flow into multiple channels in the upper thigh before entering the femoral node. Normally these have a beaded appearance in the inguinal or axillary regions due to the presence of valves. Some patients with lymphedema will demonstrate hypoplasia of the lymphatics, while others will show dilated or varicose lymphatics with or without dermal back flow, i.e., filling of the skin lymphatics (Figure 2A).

Normal and Inflammatory Lymph Nodes: The normal lymph node has a globular or kidney-shaped outline and measures approximately 1.5 cm. in its maximal dimension. The margin is frequently interrupted by a slight indentation at the hilum, where the efferent vessels can be seen leaving the node. There are generally from eight to 12 afferent vessels entering from the periphery, and fewer efferent vessels. The nodal architecture is characterized by a homogeneous reticular pattern (Figure 2B). The presence of inflammation, metastatic carcinoma, or lymphoma within the lymph node alters the normal architecture of the node. The alterations which are produced are characteristic and distinct for each of these disease entities. Acute inflammation, for example, produces an increase in the number and size of the lymph nodes in the area of inflammation. These nodes maintain their normal peripheral contour and architecture despite the enlargement.

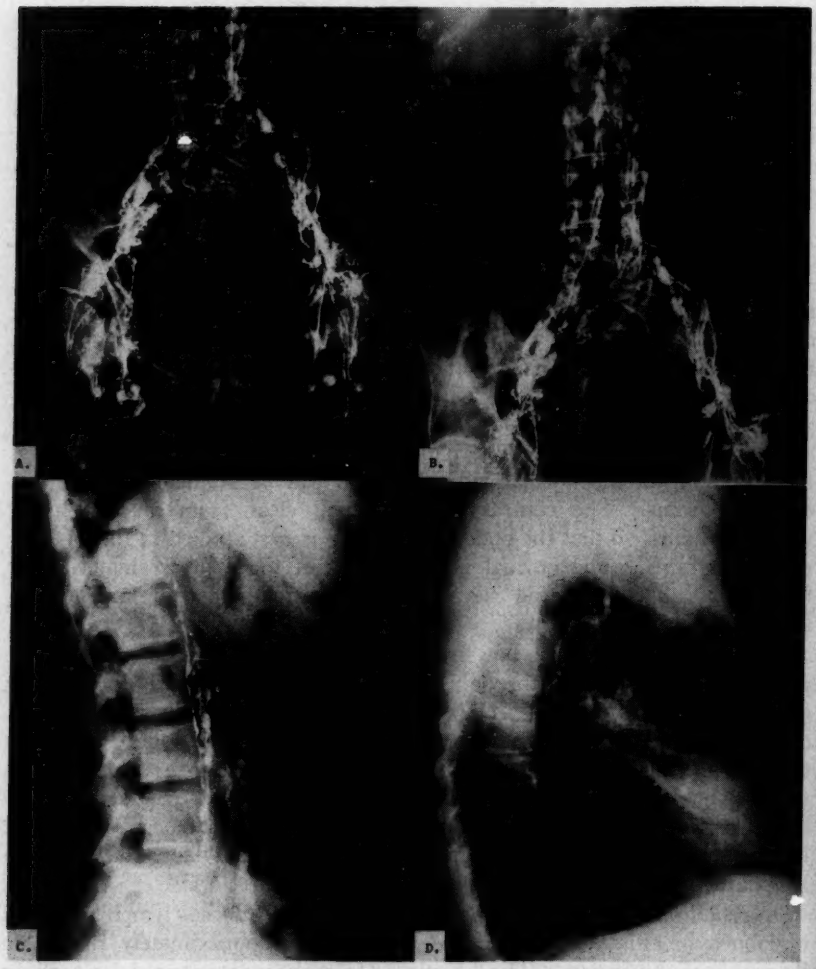

FIG 1. Normal lymphatics. A. Normal pelvic lymphatics and nodes. Note the crossing of the lymphatics to the opposite side at the sacral area. B, C. Normal lymphatics and nodes of the abdomen. Note how the lymphatics adhere closely to the anterior border of the vertebrae in the lateral view. D. Thoracic duct.

This pattern can be seen in the abdominal roentgenogram of a patient with generalized viral disease (Figure 2C).

Carcinoma: Metastatic carcinoma to the lymph nodes also produces an increase in the number and size of the nodes visualized. A characteristic pattern is produced which consists of irregular filling defects in the margin of the node. These defects give a "moth-eaten" appearance to the node. This is presumably due to embolic carcinomatous metastases. This type of

defect is amply demonstrated in the lateral abdominal roentgenogram of a 60-year-old patient with carcinoma of the rectum, which had metastasized to the retroperitoneal nodes (Figure 2D). Occasionally the carcinoma may completely replace the lymph nodes and only the deviated lymphatic vessels will reveal the presence of the enlarged nodes (Figure 6A, B).

Lymphoma: In lymphomatous disease, the lymph nodes are enlarged and have a foamy or lacy pattern which produces an almost ghost-like appearance.

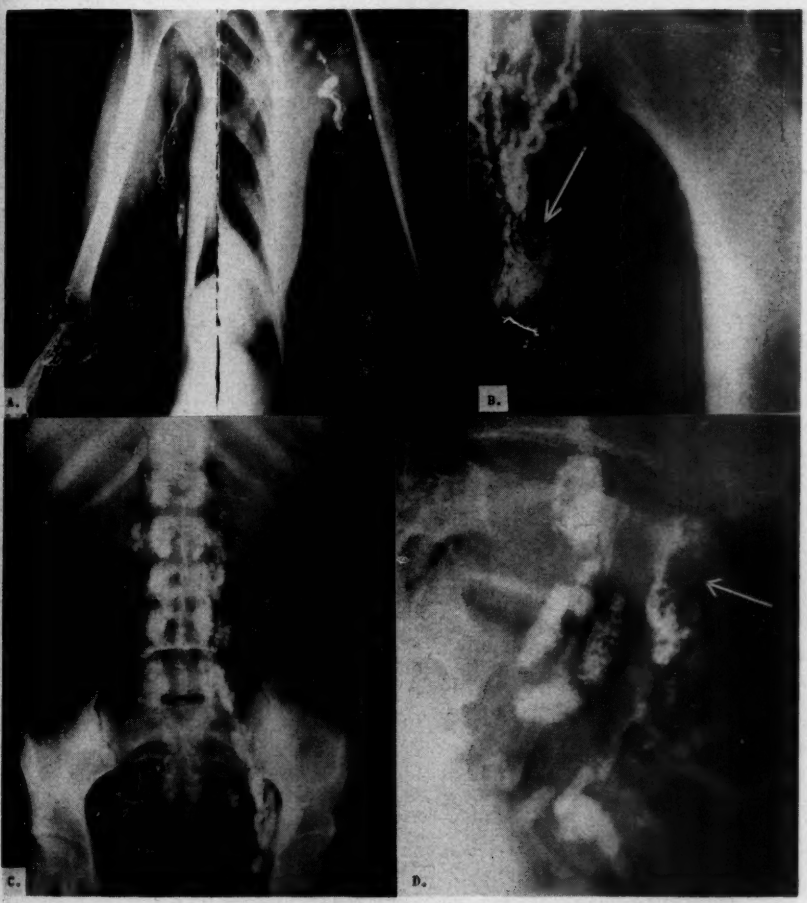

FIG. 2. A. Lymphangiogram of the arms of a patient with postmastectomy edema. Note that the edematous arm, the right, has numerous dilated, tortuous lymphatics. B. Normal lymph node. Note the even border, numerous afferent vessels entering from below, and fewer efferent leaving the hilum (arrow). C. Lymph nodes in acute inflammation. These nodes are increased in number and size, but maintain a normal architectural pattern. D. Metastatic carcinoma. Retroperitoneal nodes in a patient with carcinoma of the rectum. Note the peripheral filling defects (arrow).

In contrast to the nodes invaded by metastatic carcinoma, the outer margins of the nodes are preserved. This is consistent with the pathologic change in lymphomatous disease which originates within the node and spreads diffusely through it. Our experience suggests that some lymphomatous diseases have characteristic patterns. Nodes involved with lymphosarcoma as seen in Figure 3A, B are shown to be enlarged, their margins maintained; and they have a foamy or lacy pattern. In Hodgkin's disease, the nodal architecture as shown in Figure 3C has the same basic pattern and preserved border, with the addition of scattered, punched-out areas of replacement within the center of the node. Chronic lymphatic leukemia shows a pattern

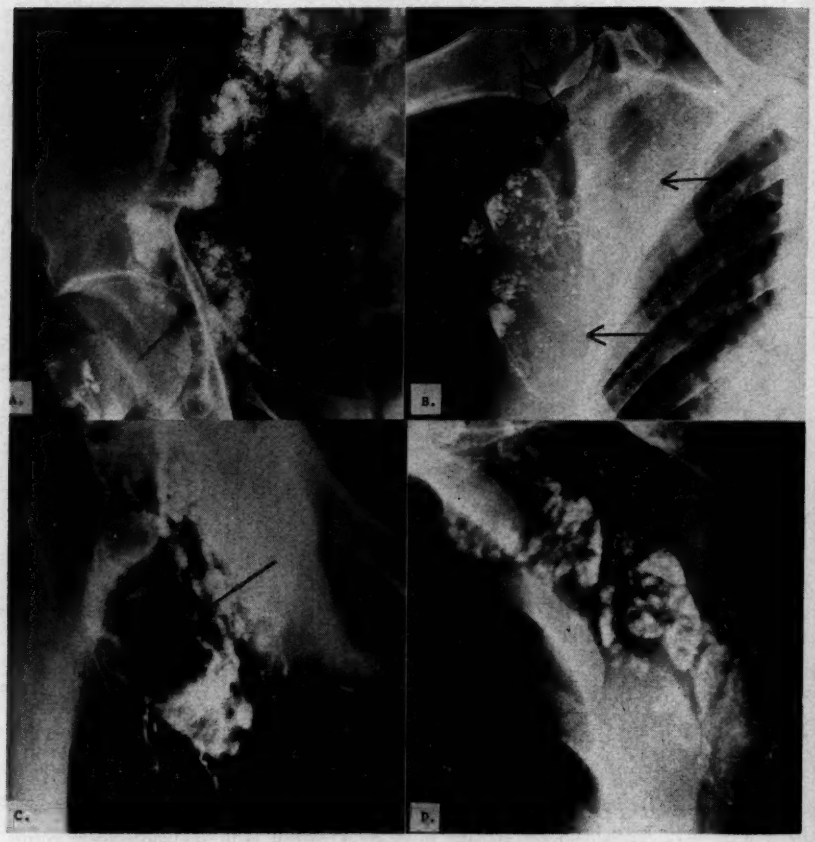

FIG. 3. Lymphomas. A. Lymphosarcoma in the iliac node. The border of the node is maintained, while the node is enlarged and has a lacy architecture. B. Advanced lymphosarcoma of the axillary nodes. Again the border is maintained but the node is grossly enlarged with a hazy, lacy pattern. C. Hodgkin's disease, showing the characteristic central punched-out area. D. Chronic lymphatic leukemia demonstrating the areas of increased collections of opaque media.

consisting of enlarged nodes which have the basic lacy architecture, continuous margins, and areas of increased collections of the opaque media (Figure 3D).

Case Reports

Some of the applications of this procedure can be illustrated in the following case reports.

A 75-year-old white male gave a history of intermittent, recurrent abdominal pain and constipation for 15 months prior to our seeing him. His abdominal pain was not severe at first, but was annoying and was associated with radiation to the back and the sacral area. The pain became more severe and on occasion was disabling. Numerous diagnostic studies were obtained including roentgenograms of the genitourinary system and the gastrointestinal tract. No mass could be felt in the abdomen and no other signs or symptoms were obtained. This man had had Paget's disease for several years, which involved the pelvis. Because of this, much of his symptomatology was thought to be referred from this area. Approximately two months prior to our seeing him, his physician noted a palpable lymph node in his left cervical area. This was biopsied twice and proved to be Hodgkin's disease. The patient was still asymptomatic except for his abdominal difficulty, and had no fever, malaise, or loss of weight. Radiation therapy was subsequently begun to the cervical area, and the question arose whether his abdominal symptoms were related to the Hodgkin's disease. His lymphangiogram graphically demonstrates the presence of far advanced lymphomatous involvement of the para-aortic nodes which project far out into the abdominal cavity (Figure 4A, B). Radiation therapy to this area relieved his symptoms. The lymphangiogram was also used as a guide to radiation portal placement in this case. It is interesting to speculate whether earlier use of this technic might have permitted an earlier diagnosis.

The second case is that of a 26-year-old white female who had had a diagnosis of Hodgkin's disease made by cervical node biopsy eight months prior to our seeing her. She had palpable cervical and supraclavicular nodes at that time and these were treated by radiation therapy, with remission of the nodes. A few weeks later she developed axillary lymphadenopathy on the right side and these nodes also responded to radiation therapy. After being in good health for five months she began to experience bouts of periodic fever and weight loss. Repeated examination over a month failed to reveal any lymphadenopathy. Because retroperitoneal involvement was suspected a lymphangiogram was performed (Figure 4C, D). The roentgenograms showed a marked increase in the number of retroperitoneal nodes and enlargement of these nodes. The nodes had a lacy pattern with discrete central punched-out areas which we considered to be typical of Hodgkin's disease. Radiation therapy was considered unfeasible in view of the widespread involvement. In this case the lymphangiogram served as a therapeutic guide as well as a diagnostic tool.

The lymphangiogram can also be of help to the surgeon, as it was in the case of a 21-year-old white male with teratocarcinoma of the left testis. After removal of the testis, a lymphangiogram was performed. The films showed a suspicious area of nodes near the left renal pelvis (Figure 5A, B, C, D). Accordingly, a radical node dissection was performed. A portable film taken at operation was not centered properly, and therefore several lymph nodes were left behind. More accurate films would have enabled the surgeon to go back, while still in the operating room, and remove the remaining nodes. This has indeed been done in subsequent cases.

Unexplained abdominal, pelvic, or back pain is frequently a problem in patients with gastrointestinal tract or genitourinary malignancy. We have frequently been able to demonstrate retroperitoneal or pelvic lymph node metastases in these patients

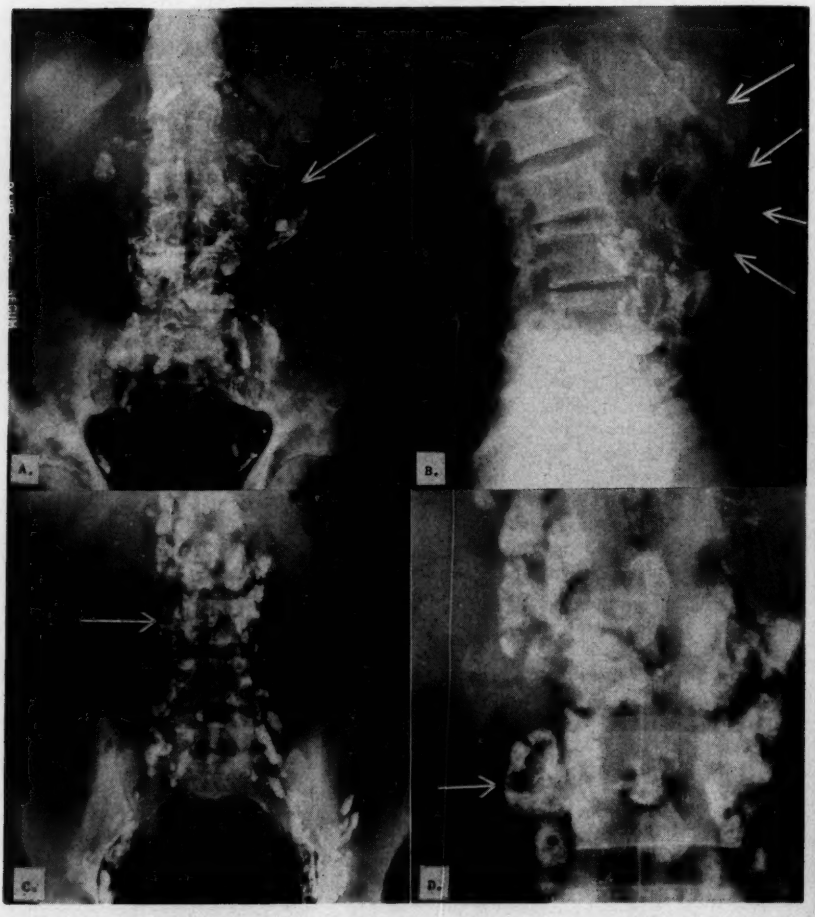

FIG. 4. A, B. Abdominal lymph nodes of a patient with advanced Hodgkin's disease (case 1). Note the extensive anterior projection of these nodes into the abdominal cavity on the lateral roentgenogram. These were not palpable. C, D. Hodgkin's disease causing fever of undetermined origin (case 2). Note the lacy architecture, increased number of nodes, and central punched-out areas (arrow).

within the area of pain. Figure 6A, B illustrates the type of findings seen in these cases. This is the abdominal lymphangiogram of a 27-year-old male with teratocarcinoma of the testis who did not have any evidence of skeletal metastases to his vertebrae but did have persistent back pain. This pain appeared to originate from the lower lumbar area. The roentgenograms demonstrate lack of filling of the lymph nodes in this area with deviation of the lymphatics around the area which should be occupied by the nodes. These nodes were completely replaced by metastatic carcinoma and therefore were not visualized by our technic. Radiation therapy to these nodal areas, or systemic chemotherapy, will often relieve the patient of this most distressing symptom.

A final case illustrates an unusual finding in congenital lymphedema. A 17-year-old white female gave a four-year history of bilateral lower extremity edema. There was no history of trauma or infection in either lower extremity. There was no family history of lymphedema. A lymphangiogram did not show any gross abnormalities in the lymphatics of the lower extremities themselves. However, there was an area in the region of the fourth lumbar vertebrae which showed a collection of tortuous, dilated lymphatics (Figure 6C, D). This abnormality has been seen one other time in our series and has not been reported elsewhere. Perhaps this

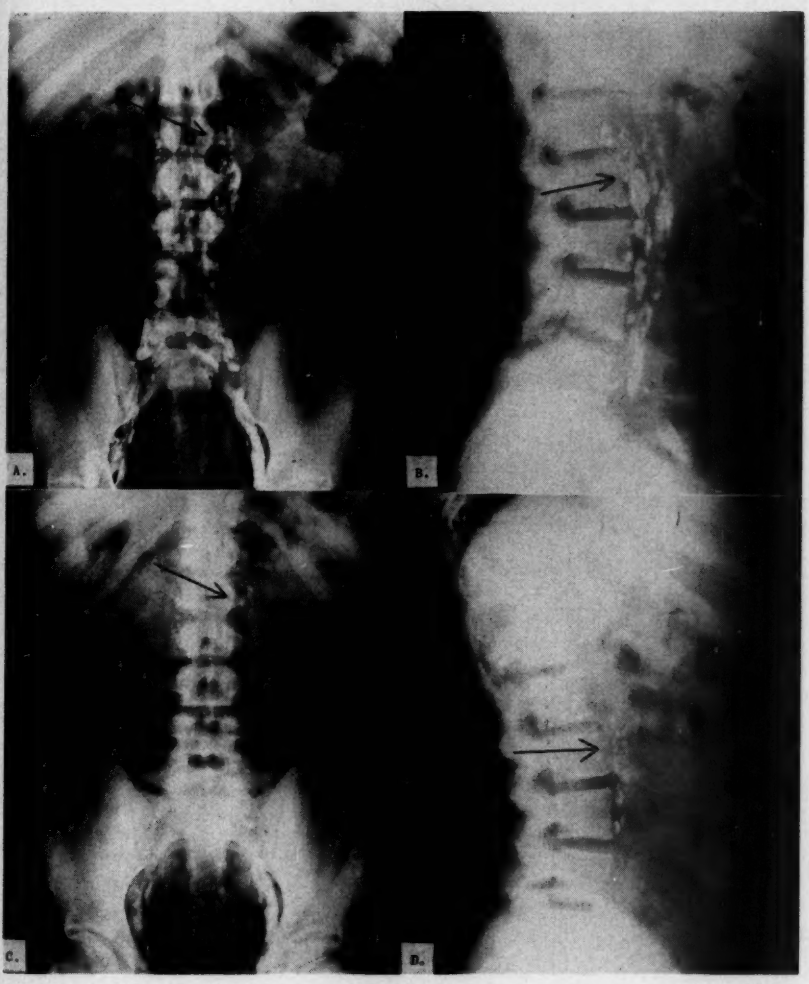

FIG. 5. The use of the lymphangiogram in surgery. Fig. 5A, B are the preoperative roentgenograms of a patient with teratocarcinoma of the left testis. The nodes in the left renal pelvic area appear suspicious (arrow). In the postoperative films, Fig. 5C, D, it is seen that these same nodes were left behind despite a competent attempt at radical excision.

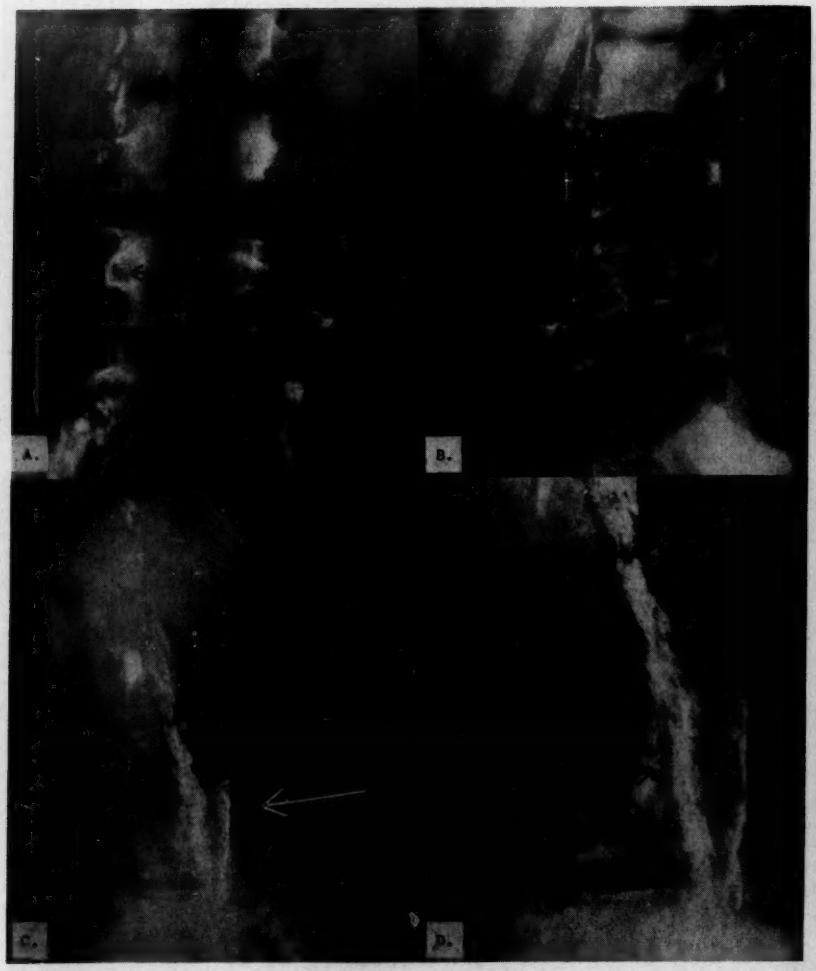

FIG. 6. A, B. These films show abdominal metastases from a testicular tumor which completely replace the nodal tissue (case 5). The nodes are not visualized, but the lymphatics are seen to be deviated around the areas of nodal replacement (arrow). C, D. Abnormal abdominal lymphatics in a patient with bilateral lymphedema. The close-up shows this to be an area of tortuous, dilated lymphatics which projected into the abdominal cavity.

represents a local lesion similar to a lymphangioma, and the possibility of surgical correction can be entertained.

DISCUSSION

The above are but a few of many cases in which the lymphangiogram has been an important diagnostic tool. More exact location of tumor site, demonstration of unsuspected disease, or of unsuspected extension of malignancy

are important advantages to be derived from the use of this procedure. As a guide to the surgeon, it can be used to determine the feasibility of radical surgery. Even areas of relative accessibility, such as the axilla when dealing with breast carcinoma, have been shown to contain lymph nodes which are actually far out of reach of the palpating fingers. When these nodes can be shown to contain carcinoma, radical surgery would seem to be

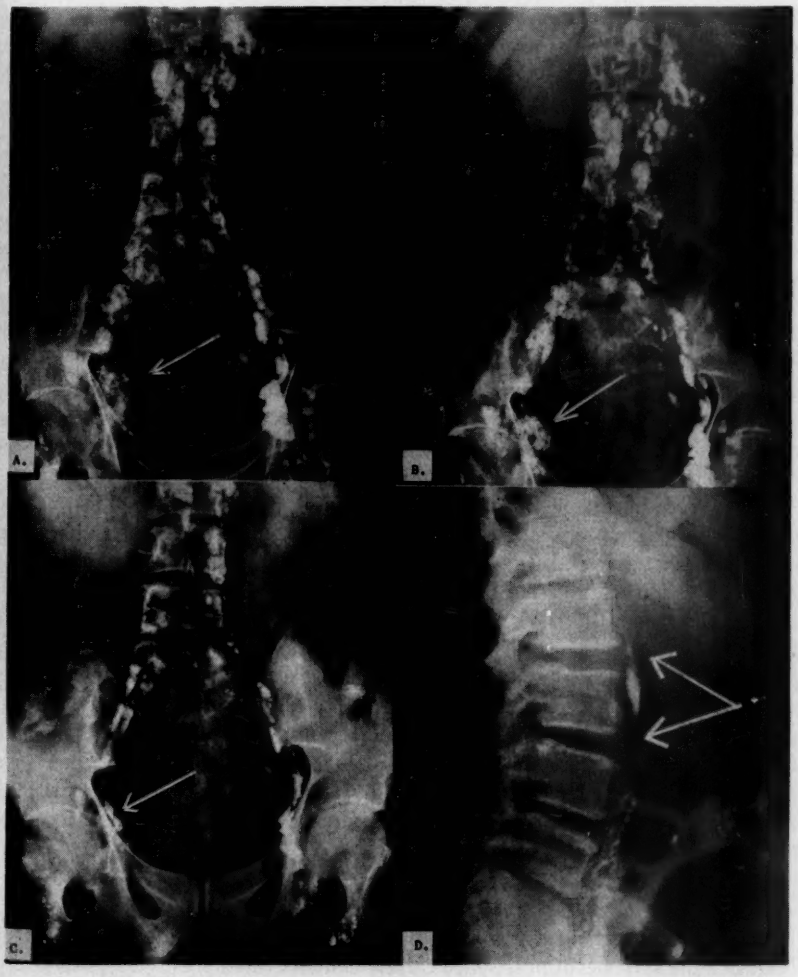

FIG. 7. A, B, C. Remission of lymphosarcoma following chemotherapy. Fig. 7A shows the nodes prior to therapy. Six days after therapy the nodes are reduced in size (7B). Fig. 7C was taken six months later and shows continued remission of the nodes. D. Carcinoma of the body of the pancreas. Note the absence of filling of the lymphatics in the upper lumbar area (arrows).

contraindicated. If surgery is performed, portable or postoperative films can be used to assess the degree of completion of the procedure.

The lymphangiogram has also served as a therapeutic aid with which to follow the progress of nodal malignant disease in patients treated with radiotherapy or chemotherapy. Figure 7A shows the lymphangiogram of a patient with lymphosarcoma who received systemic chemotherapy with an alkylating agent. Note the marked reduction in nodal size six days after institution of therapy (Figure 7B). A film taken six months later (Figure 7C) without further injection of contrast material, shows that the disease is still under control. It is important to note that although the nodes have reduced in size, their basic outline has remained the same, indicating true nodal shrinkage rather than simple loss of contrast material.

Unexpected benefits may occur, as is demonstrated by the case of a 52-year-old colored male with carcinoma of the body of the pancreas. His lymphangiogram shows absence of filling of the lymphatics or nodes in the upper lumbar area, although the thoracic duct and supraclavicular nodes were filled and no metastatic nodal disease was seen (Figure 7D). A similar pattern has been seen in two other cases of pancreatic carcinoma. Although it is too early to attribute positive significance to this finding it is interesting to suggest that it may be of diagnostic aid in a difficult problem. Lastly, the lymphatic cannula has been used to introduce chemotherapeutic agents into a few patients following demonstration of malignant nodal disease. Our results have not been very rewarding to date but we are continuing this study.

The procedure itself has not caused any serious complications in our 140 cases. Approximately six of our patients developed symptoms when some of the contrast material was overzealously forced via the venous system into the lungs. This can be seen as fine pulmonary embolization.[10] Temperature elevation was usually the only symptom but one patient had a cough and a brief episode of dyspnea. These symptoms responded to bed rest in from two to three days, and the contrast material cleared from the lungs within a week. Histologic examination of the nodes within a few days of the procedure has revealed the presence of foreign body reaction (lipogranuloma) to the oil. The significance of this is not known at this time. No physiologic change has been produced by the procedure and repeat studies after 10 months have not demonstrated any nodal changes which could be ascribed to the previous study.

Summary

Utilizing direct intralymphatic injection of contrast material, the lymph nodes of the retroperitoneal space can be demonstrated roentgenographically. A variety of findings is seen. Normal nodes exhibit a homogeneous reticular pattern. Inflammation causes nodal enlargement without disruption of the normal pattern. Metastatic carcinoma causes partial nodal re-

placement at the margin with a "moth-eaten" appearance, whereas lymphoma produces an enlarged node with a lacy, diffusely infiltrative pattern. The procedure has practical diagnostic application as well as a role in directing and evaluating therapy.

ACKNOWLEDGMENTS

The authors would like to express their appreciation to Dr. Phillip Hodes, Dr. Bernard P. Widman, and Dr. Stanley Dische for their guidance in this study.

SUMMARIO IN INTERLINGUA

Lymphangiographia es un nove technica pro le visualisation roentgenographic del systema lymphatic. Nos ha utilisate iste methodo diagnostic in 140 casos. Illo consiste in delinear le lymphaticos del dorso del pede per medio de un colorante colloide blau, in isolar e cannular le lymphatico, e in injicer un medio de contrasto radio-opac ad in le lymphaticos. Le methodo permitte le delineation del lymphaticos del extremitates, del pelve, e del abdomine e etiam del nodos pelvic e retroperitonee. Le medio de contrasto, que es oleose, persiste durante sex septimanas o plus e assi permitte le observation del progresso del morbo.

Le vasos e nodos lymphatic exhibi un constante configuration e architectura in le subjecto normal, sed illos es alterate in morbos que affice ille vasos e nodos. In le presentia de lymphedema, le lymphangiogramma monstra alterationes de varie generes, ab hypoplasia usque ad le visualisation de numerose dilatate lymphaticos collateral. Morbo inflammatori produce simple hyperplasia nodal. Carcinoma metastatic produce irregular defectos de replenation peripheric in le visualisate nodos. Lymphomas causa allargamento del nodos, con un characteristic configuration architectural del apparentia de dentellas de Bruxelles.

Lymphangiographia es de beneficio clinic in le diagnose de morbo retroperitonee. Lesiones in iste area ha essite notate como causas de varie problemas clinic, incluse constipation con dolor abdominal, febre non diagnosticate, dolor de dorso, e obscur dolores abdominal. Post le establimento del diagnose, le lymphangiogramma pote esser de valor pro le chirurgo como guida in le dissection de nodos lymphatic. Le porta pro le tractamento radiotherapeutic pote esser localisate plus precisemente per medio de lymphangiographia, e le radiotherapeuta e le chimotherapeuta pote sequer le effecto del therapia in morbo nodal per medio del lymphangiographia.

In le casos studiate, complicationes esseva infrequente e minor. Nulle alterationes physiologic ha occurrite post lymphangiographia, e repetitiones del studios post intervallos de dece menses ha revelate nulle alteration in le systema lymphatic.

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RENAL AMYLOIDOSIS *

By ROBERT D. LINDEMAN, M.D., ROBERT L. SCHEER, M.D., and LAWRENCE G. RAISZ, M.D.,† *Syracuse, New York*

THE effect of amyloid deposition in the kidneys often provides the first, and sometimes the sole, clinical clue to the presence of this disorder. The technic of needle biopsy of the kidney has helped to clarify the place of amyloidosis in the spectrum of renal disease and is of particular importance in the differential diagnosis of the nephrotic syndrome.[1-3] In order to gain a better understanding of the renal involvement in amyloidosis, we have reviewed the 17 cases seen at this center from 1954 to 1960. Fifteen patients showed evidence of renal disease. Eight cases presented findings of particular interest and will be presented in detail.

CASE REPORTS

Case 1. A 25-year-old white male laborer was admitted to the Syracuse University Hospital in April, 1957, because of swelling of the abdomen. During the previous six months, he had noticed mild exertional dyspnea, nocturia, and a weight loss of 12 pounds. Two months before admission, he had had a sore throat and anorexia, followed by swelling of the abdomen and passing of "brown" urine. The only significant illness in the past was an episode of bilateral painless swelling of the knees which occurred in the previous year.

At the time of admission, his temperature was 99.6° F., pulse 92, and blood pressure 130/74 mm. Hg. The patient appeared to be chronically ill and underweight. The posterior pharynx was injected and some whitish-yellow exudate was present. There were ascites, leg edema, and hepatosplenomegaly.

The blood count was normal. The urine gave a 4-plus test for protein and the sediment contained rare hyaline casts and doubly refractile bodies. Blood Wasserman was negative. The serum nonprotein nitrogen, creatinine, fasting glucose, and electrolyte values were all normal. The serum albumin was 2.4 gm.; globulin, 1.9 gm./100 ml. Paper electrophoresis of the serum showed an elevation of the $alpha_2$ globulin. A 24-hour urine specimen contained 13 gm. of albumin on admission and 5.1 gm. two weeks later. A urine test for Bence Jones protein was negative. The serum cholesterol was 344 mg./100 ml. There were minimal abnormalities of the cephalin flocculation and thymol turbidity, but all other liver function tests were normal. Bone marrow aspiration and several preparations of blood and bone marrow for lupus erythematosus cells were negative. Roentgenograms of the chest, bones, and kidneys were normal. There was 45% retention of Congo red dye in the serum one hour after injection. Biopsies of the liver, skin, and muscles stained with hematoxylin and eosin, as well as with crystal violet, were normal. Needle biopsy of the kidney showed small deposits of amyloid in the glomeruli (Figure 1A).

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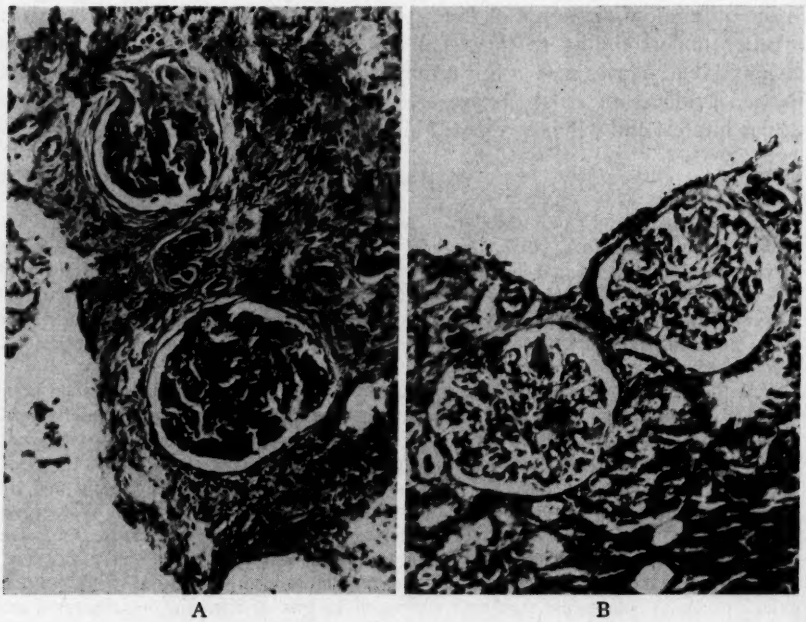
Diuresis started promptly and vigorously when the patient was given a sodium-restricted (800 mg.) diet. On the sixth hospital day, an erythematous rash appeared on the "butterfly" area of the face and lasted two days. A month later, the patient was free of edema and discharged without dietary restrictions or medication.

Two months after his admission to the hospital, a blood Wasserman titer of over 200 was obtained. This was confirmed by repeated tests. A lumbar puncture was negative. In September, 1957, a treponema immobilization test was positive. The patient was then given two courses of penicillin therapy.

In May, 1958, the patient was readmitted to the Syracuse University Hospital for re-evaluation. He was asymptomatic and the physical examination demonstrated only the previously noted hepatosplenomegaly. The urine gave a 3-plus test for



A B

FIG. 1. A and B. Renal biopsy specimens from case 1, stained with hematoxylin and eosin. Specimen A was obtained during the first hospitalization and specimen B was obtained one year later when the patient was asymptomatic. Both specimens show a similar degree of patchy deposition of amyloid in the glomeruli.

protein. The serum albumin was 5.1 gm.; globulin, 1.8 gm./100 ml. A second renal biopsy showed persistence of amyloid deposits (Figure 1B).

The patient returned to his job, one requiring hard manual labor, and remained well. In April, 1959, he left Syracuse and was lost to follow-up.

Comment: This young man with nephrotic syndrome was found to have minimal renal amyloidosis by renal biopsy. We have assumed that primary amyloidosis was the cause of the nephrotic syndrome. It is only if we assume that the original serologic test for syphilis was in error that syphilis can be considered as an alternative etiology for the nephrotic syndrome.

Amyloidosis in this patient presumably was not secondary to syphilis since this combination is associated with active tertiary lues.

The patient had a clinical remission of his nephrotic syndrome, but a second renal biopsy failed to show corresponding morphologic improvement. Since liver histology was normal, it is difficult to assess the significance of the persistent hepatosplenomegaly. In this case, renal biopsy established the diagnosis of amyloidosis.

Case 2. A 53-year-old white male was admitted to the Syracuse University Hospital in January, 1958, with abdominal distress and vomiting. The patient had had intermittent diarrhea for the last 10 years. Eighteen months prior to admission, he noticed abdominal distention, fatigue, anorexia, and weight loss. Later, he was troubled by pain and cramps in the extremities, urinary frequency, and nocturia. Four months before being seen here, the patient was referred to another hospital. At that time, the urine gave a 4-plus test for protein and the sediment contained hyaline and granular casts. The serum protein was 4.6 gm./100 ml.; the cholesterol, 907 gm./100 ml. The nonprotein nitrogen, creatinine clearance, and intravenous pyelogram were normal. A bone marrow aspirate contained an increased number of lymphocytes and a few abnormal appearing plasma cells. The beta globulin fraction of the serum was found to be elevated by electrophoresis. A needle biopsy of the kidney showed extensive amyloid deposits in the glomeruli.

Subsequently, the patient's symptoms became worse, and in addition he experienced numbness and tingling in the extremities and stumbled when walking. Peripheral edema first appeared a few weeks before admission.

On admission here, the patient appeared to be thin and chronically ill. The blood pressure was 95/60 mm. Hg. Muscular atrophy was striking. The deep tendon reflexes were hypoactive and position and vibratory senses were diminished. Neither liver nor spleen was palpable. Pitting edema of the legs was present.

The blood count and serum electrolyte concentrations were normal. A 24-hour urine specimen contained 3.1 gm. of protein. The nonprotein nitrogen was 65 mg.; serum albumin, 2.2 gm.; globulin 1.2 gm./100 ml. The serum cholesterol was 1,070 mg./100 ml. A complete radiologic examination of the gastrointestinal tract was negative. Diuresis was attempted with prednisone without success, and the patient was discharged after two weeks. He died two months later. Post-mortem examination was not obtained.

Comment: A renal biopsy established the diagnosis of amyloidosis at a time when the clinical findings were limited to early peripheral neuropathy, unexplained gastrointestinal complaints, and proteinuria. In retrospect, the clinical course was consistent with primary amyoidosis. Despite the equivocal bone marrow picture, multiple myeloma appears unlikely in this case in the absence of abnormal proteins in the serum or Bence Jones protein in the urine.

Case 3. A 56-year-old, white male metal plater was admitted to the Syracuse Veterans Administration Hospital in January, 1956, in acute urinary retention. This patient had suffered painful cervical lymphadenopathy, weakness, and weight loss for two and one-half years. The diagnosis of amyloidosis was established by cervical node biopsy. One year prior to admission, a radical neck dissection was performed at another hospital in an effort to alleviate the pain. At that time, he had hepatomegaly, but only a trace of albumin in the urine. He was readmitted to the same

hospital nine months later because of dysuria. He was found to have bilateral renal calculi and a 2 cm. submucosal mass in the neck of the bladder. Pathologically, this proved to be a collection of amyloid. Laboratory studies during that hospitalization, which included cultures for tuberculosis, were negative.

On admission here, the patient was in acute urinary retention. He had an acute lower urinary tract infection as well as benign prostatic hypertrophy.

The hematocrit was 36%, the white blood cell count, 20,400/cu. mm., with 85% neutrophils. The urine gave a 3-plus test for protein and the urine sediment contained many white cells and red cells per high power field. The nonprotein nitrogen was 51 mg. and the serum creatinine 5.1 mg./100 ml. The serum electrolytes were normal. The serum albumin was 3.8 gm., the serum globulin 3.3 gm./100 ml. Paper electrophoresis of the serum showed a localized accumulation of a discrete component in the gamma globulin fraction suggestive of multiple myeloma. There was no Bence Jones protein in the urine. Two examinations of the sternal marrow were normal. An intravenous pyelogram revealed parenchymal calcifications in both kidneys and marked distortion of the calyces. *Escherichia coli* was cultured from the urine.

The patient was discharged after treatment for urinary tract infection. The appearance of cough, dyspnea, orthopnea, and ankle edema led to readmission in October, 1956, at which time bilateral pleural effusion was found. The urine gave a 3-plus test for protein. The serum albumin was now 2.8 gm., the globulin 2 gm./100 ml. Terminally, the nonprotein nitrogen rose to 108 mg./100 ml. The patient died in January, 1957.

Post-mortem examination revealed widespread amyloid infiltration involving the heart, lungs, serosal surfaces, spleen, lymph nodes, gastrointestinal tract, liver, adrenals, kidneys, ureters, and bladder. Deposits of amyloid had partially obstructed the left ureter. There was severe pyelonephrosis on the left. Both kidneys contained large deposits of amyloid in the interstitial spaces, but there was appreciably more amyloid in the glomerular tufts of the left kidney.

Comment: This case is a striking example of the multiple systemic involvement seen in primary amyloidosis. The severe, painful lymphadenopathy is an unusual feature. Renal amyloidosis, as evidenced by the nephrotic syndrome, became manifest only late in the course of the patient's illness, and even then was overshadowed by infection. It is interesting to note that there was more amyloid in the glomeruli of the more severely infected kidney. We were unable to confirm the diagnosis of multiple myeloma despite a serum electrophoretic pattern typical of this disorder.

Case 4. A 56-year-old white housewife was first seen at the Crouse Irving Hospital in July, 1957, with chief complaints of dyspnea and orthopnea. The patient's illness began in May, 1957, when she was confined to her home with bilateral bronchopneumonia, followed by dyspnea, orthopnea, leg edema, and a weight loss of 40 pounds.

When admitted to the hospital, the patient appeared to be chronically ill. The outstanding findings were pleural effusion in the right hemithorax, hepatomegaly, and marked edema of the legs and presacral area.

The blood count was normal. The urine gave a 2-plus test for protein, and there were severe pyuria and microscopic hematuria. The serum nonprotein nitrogen, fasting glucose, cholesterol, and proteins were normal. Roentgenograms of the chest showed unilateral pleural effusion and cardiomegaly. The electrocardiogram was interpreted as showing atrial fibrillation and an old myocardial infarction.

Thoracentesis, digitalis, and diuretics produced symptomatic relief, and the patient left the hospital contrary to the advice of the medical staff.

In September, 1957, progression of dyspnea necessitated readmission to the hospital. She now appeared emaciated and was severely dyspneic. Her blood pressure was 80/60 mm. Hg. Edema now extended over the abdominal wall. There were massive ascites and right pleural effusion.

The white blood cell count was 29,200/cu. mm., with 97% neutrophils. There was only a trace of urinary protein. The serum albumin was 3.3 gm., the globulin 3.5 gm./100 ml. The nonprotein nitrogen and serum electrolytes were normal except for the CO_2, which was 18 mEq./L. The patient died 18 hours after admission.

The post-mortem examination revealed massive pneumonia of the right lung accompanied by pulmonary edema and diffuse pulmonary fibrosis. The heart weighed 450 gm. and a large healed myocardial infarction was present. There was marked amyloid involvement of the heart, as well as some deposits in the liver, spleen, and adrenals. The kidneys showed small amounts of amyloid in the glomeruli.

Comment: We have assumed that this patient had primary amyloidosis with major involvement of the heart. This organ had been damaged previously, which may have predisposed it to amyloid infiltration. Amyloid deposits confined to the heart alone have been reported in elderly patients and are often associated with prior cardiac damage.[4-6] Our patient differed from this group in that she was younger and showed a wider distribution of amyloid. We considered the possibility that this patient may have developed amyloidosis secondary to her severe pulmonary infection. The relatively short duration of that infection, as well as the predominant cardiac involvement, makes secondary amyloidosis less likely. Sparse deposits of amyloid were found in the kidneys, and there was correspondingly little clinical evidence of renal disease.

Case 5. A 67-year-old retired white male farmer was admitted to the Syracuse Veterans Administration Hospital in December, 1956, for treatment of a toxic goiter. He was given a therapeutic dose of 9.7 μc. of I^{131} and discharged.

After an initial clinical improvement, the patient noticed hoarseness, weakness, easy bruising, and recurrent weight loss. He was again referred to this hospital in May, 1959.

On this admission, the patient appeared mentally dull and had a hoarse voice. The skin was dry with a yellowish tint and he had many purpuric lesions. The liver, but not the spleen, was palpable. The relaxation phase of the deep tendon reflexes was prolonged.

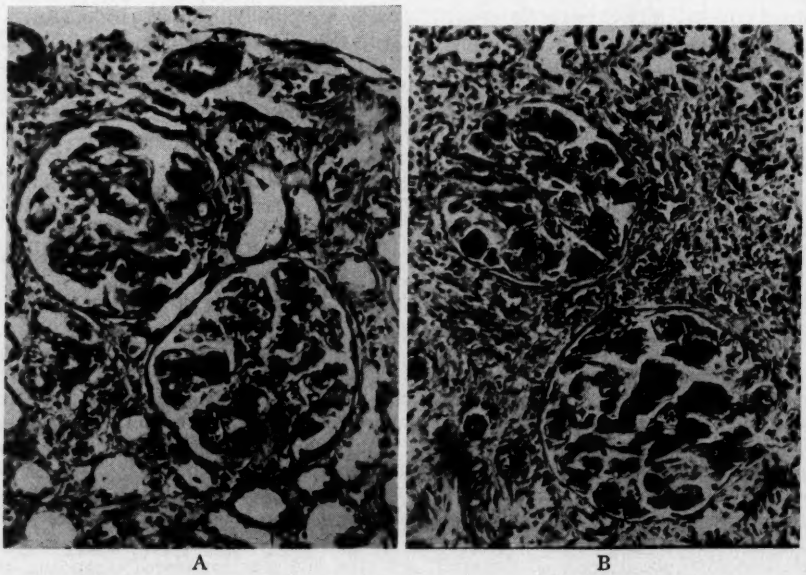
The hematocrit was 26%. The white blood cell count, platelet count, serum iron and iron binding capacity, and bleeding and clotting times were all normal. The urine gave a 3-plus test for protein and the sediment contained many granular casts. The nonprotein nitrogen was 130 mg., the serum creatinine, 11.4 mg./100 ml. The serum albumin was 3.4 gm., the globulin 2.6 gm./100 ml. Paper electrophoresis of the serum proteins was normal. The serum cholesterol was 496 mg./100 ml. The serum electrolytes were normal, except for the CO_2-combining power of 19 mEq./L. Bromsulfalein retention was 47% in 45 minutes. The protein bound iodine was 1.3 μg./100 ml. and the thyroid uptake of I^{131} was 1% in 24 hours. A bone marrow aspirate showed 95% plasma cells of the small cell type and was considered diagnostic of multiple myeloma.

A week after admission, the patient became comatose. He was given intravenous tri-iodothyronine and hydrocortisone, but died two days later.

The post-mortem examination confirmed the presence of multiple myeloma in the bone marrow. There was moderate to marked amyloid involvement of every organ of the body. The thyroid in particular was almost completely replaced by amyloid. There was moderately severe amyloid infiltration of the kidneys, as well as arterial and arteriolar nephrosclerosis.

Comment: The widespread distribution of this patient's amyloidosis suggests that multiple myeloma, rather than myxedema, was the inciting factor, although both diseases may ultimately have contributed to the progression of the amyloidosis. The amyloidosis was probably more responsible for the development of myxedema than was the dose of I^{131}, since amyloid had replaced most of the thyroid tissue. Severe amyloidosis of the thyroid is sufficiently unusual [7] that we again call attention to the possible predilection of amyloidosis for a previously injured organ, in this case the irradiated thyroid. Such advanced infiltration of the kidneys is unusual in cases of amyloidosis associated with multiple myeloma. The patient did not develop the nephrotic syndrome but presented with severe renal failure. Arteriolar nephrosclerosis may also have contributed to renal failure in this case.

Case 6. A 57-year-old white housewife was admitted to the Crouse Irving Hospital in August, 1957, because of progressive leg edema. The patient had had rheumatoid arthritis for 12 years. Hydrocortisone was started three years prior to admission. Glycosuria had developed, but attempts to discontinue steroid therapy



A B

FIG. 2. A and B. Renal biopsy specimen (A) and autopsy specimen (B) from case 6, stained with hematoxylin and eosin. Both specimens show extensive amyloid infiltration of the glomeruli.

were unsuccessful and she was given tolbutamide. Leg edema developed 15 months prior to admission.

On admission, the patient appeared to be chronically ill. There were deformities characteristic of advanced rheumatoid arthritis. The liver and spleen were not palpable. There was marked pitting edema of the legs.

The hematocrit was 36%. The urine gave a 4-plus test for protein, a trace test for glucose, and the sediment contained 8 to 10 white blood cells per high power field. A 24-hour urine specimen contained 4.2 gm. of protein. The fasting blood glucose and nonprotein nitrogen were normal. The serum albumin was 1.9 gm., the albumin 2.5 gm./100 ml. Serum electrolytes were normal. Two preparations of blood for lupus erythematosus cells were negative. A needle biopsy of the kidney revealed amyloidosis (Figure 2A).

The patient was discharged on chlorothiazide therapy, but the edema gradually reaccumulated. In December, 1957, the patient was admitted to the Syracuse University Hospital with nausea, vomiting, and diarrhea. She now appeared pale, her eyelids were puffy, and she had ascites.

The hematocrit was 27%. During this hospitalization, the average 24-hour urine protein excretion was 9 gm. The nonprotein nitrogen was 55 mg./100 ml. The serum albumin remained at 1.9 gm., but the globulin was now 1.3 gm./100 ml. The serum electrolytes were normal.

The patient was discharged after diuresis resulted in a weight loss of 20 pounds.

In April, 1958, the patient was readmitted to the Crouse Irving Hospital in a preterminal state. The nonprotein nitrogen was 168 mg./100 ml., the CO_2-combining power, 10 mEq./L. The patient died four days later.

At post-mortem examination there was marked amyloid infiltration of the spleen, adrenals, and kidneys. There was heavy deposition of amyloid in both renal arterioles and glomeruli with associated tubular atrophy (Figure 2B).

Comment: This patient developed clinical evidence of amyloidosis while on continuous steroid therapy for rheumatoid arthritis. Compared with the renal biopsy specimen, a post-mortem specimen obtained eight months later showed little histologic progression (Figure 2A, B), although the patient developed renal failure during this period. On several occasions, discontinuation of steroid therapy resulted in weakness, postural hypotension, and vomiting, suggesting adrenal insufficiency. The finding of almost complete replacement of the adrenals with amyloid at post-mortem supported this clinical impression.[8]

Case 7. This 41-year-old white male artist was admitted to the Syracuse University Hospital in November, 1953, for evaluation of proteinuria. He had developed tuberculosis at age 18, which became inactive after the age of 28. Bilateral cataracts appeared when the patient was in his early twenties. In the six years preceding his admission, he had been troubled with indolent leg ulcers and muscle cramps. Several months before admission, he noted urinary frequency and nocturia.

One brother had a physical habitus similar to that of the patient. Another brother had pulmonary tuberculosis.

The patient was five feet tall and weighed 78 pounds. He had sparse gray hair, a "bird-like" facies, and appeared considerably older than 41. He was alert and intelligent. His voice was high-pitched and hoarse. The skin over his face and legs was tight and thin. There was slight hepatomegaly. The feet showed multiple ulcerations and decreased arterial pulsations.

The hematocrit was 39%. The urine gave a 3-plus test for protein and the

sediment contained granular and hyaline casts. A 24-hour urine specimen contained 7 gm. of protein. The fasting glucose and glucose tolerance tests were normal, and the nonprotein nitrogen was 51 mg./100 ml. The serum albumin was 3.9 gm., the globulin 2.2 gm./100 ml. The serum cholesterol was 703 mg./100 ml. The urea clearance was 76 ml./min. Serum concentrations of calcium, phosphorus, and the electrolytes were normal. Alkaline phosphatase was 13.4 Bodansky units. Urinary Sulkowitch tests were negative and the 17-ketosteroid excretion was normal. The electrocardiogram was compatible with left ventricular enlargement. Roentgenograms of the chest revealed extensive pleural thickening on the right and old fibrocalcific tuberculosis in both upper lobes. Roentgenograms of the bones, gastrointestinal tract, and urinary tract were normal except for some soft tissue calcifications in the feet. A skin biopsy showed epidermal atrophy. Sputum cultures were negative for acid-fast bacilli.

In May, 1954, the patient was admitted to the Crouse Irving Hospital after a brief illness and was found to have an extensive pneumonia on the right side. The hematocrit was 26%, the white blood cell count 54,800/cu. mm., with 96% neutrophils. The nonprotein nitrogen was 108 mg./100 ml. The patient died 48 hours after admission.

Complete consolidation of the right lung and a 7 cm. abscess in the upper lobe were found at autopsy. There was also a pleural effusion on the right and evidence of old tuberculosis bilaterally. There was advanced generalized arteriosclerosis. The pituitary gland and the testes were atrophied. Severe amyloid infiltration was found in the liver, spleen, adrenals, and kidneys.

Comment: This patient had premature cataracts, leg ulcers, and the characteristic habitus and skin, hair, and voice changes of Werner's syndrome. Amyloidosis may have been related to the longstanding, apparently healed tuberculosis, or to the leg ulcers. It is also possible that Werner's syndrome might be a separate cause of amyloidosis. Despite the severe renal involvement found at post-mortem, the patient did not develop the nephrotic syndrome and renal failure was a terminal event.

Case 8. This 49-year-old white female alcoholic was admitted eight times to the Onondaga County Tuberculosis Sanatorium between November, 1949, and her death in January, 1958. Far advanced pulmonary tuberculosis with bilateral cavitation was present on the first admission. The sputum remained positive for acid-fast bacilli despite treatment with collapse therapy and antituberculosis drugs. In 1952 proteinuria was first discovered. In 1956 the urine reaction for protein was repeatedly 4-plus, and the sediment contained many white blood cells per high power field. Thereafter, the serum albumin decreased from 3.5 to 1.9 gm., and the globulin increased from 2.7 to 4.5 gm./100 ml. In 1957 the blood urea nitrogen rose from 23 to 42 mg./100 ml., and the CO_2-combining power fell to 10 mEq./L. The other electrolytes were normal. During the patient's terminal illness the urine was alkaline, and acidosis persisted despite the oral administration of large amounts of sodium bicarbonate.

Post-mortem examination revealed, in addition to the extensive pulmonary tuberculosis, heavy amyloid deposits in the liver, adrenals, and kidneys. There was also minimal chronic pyelonephritis.

Comment: This patient had renal amyloidosis secondary to intractable tuberculosis. Initially, this presented as a nephrotic syndrome. Subsequently, she developed severe acidosis which seemed out of proportion to

nitrogen retention. It is unlikely that the minimal pyelonephritis found at autopsy was responsible for this defect.

Discussion

The data on the foregoing patients and on seven additional patients with amyloidosis and renal disease are summarized in Table 1. Only two patients with amyloidosis were found to be free of renal disease. In one case of multiple myeloma with amyloid involvement of the tongue, a renal biopsy obtained six months prior to death showed tubular obstruction by precipitated protein, but no amyloid. The other case was a patient whose peripheral neuropathy had been proved to be due to amyloidosis. This man is still alive and has no clinical evidence of renal disease. A renal biopsy has not been done.

Thus, renal amyloidosis was present in 15 of 17 patients. The incidence cited in the literature ranges from 27% in primary amyloidosis [7] to 83% in amyloidosis secondary to tuberculosis.[9] Ten of our cases had the typical nephrotic syndrome. Although associated findings often suggested the possibility of amyloidosis in these patients, the renal disease was indistinguishable from that seen in other forms of the nephrotic syndrome. Other workers, using renal biopsies, have emphasized the importance of amyloidosis as a cause of the nephrotic syndrome in adults.[1-3] Renal biopsy provided means of making a definitive diagnosis in cases 1, 2, 6, and 8, and appears to be a safe procedure in amyloidosis.[1-3, 10-13] The subsequent course of renal amyloidosis is generally similar to that of other occlusive glomerular diseases. However, in contrast to chronic glomerulonephritis, we have observed that in amyloidosis there may be no lessening of proteinuria and no increase in serum albumin as glomerular obstruction progresses to uremia. The progression of renal failure in amyloidosis is relatively rapid and prolonged periods of stable, compensated azotemia are seldom observed. Occasionally, patients with renal amyloidosis proceed to renal failure without having gone through a nephrotic phase (cases 5, 7).[14] Hypertension is unusual. Only one patient in this series (case 9) developed an elevated blood pressure.

The pathogenesis of the nephrotic syndrome in renal amyloidosis has recently been re-examined on the basis of electron microscopic findings.[15-17] Amyloid is deposited first on the endothelial surface of the basement membrane. As the lesion becomes more extensive, the basement membrane may be penetrated and replaced by a structurally less compact amyloid substance presenting less of a diffusion barrier to plasma proteins. Others feel that amyloid may be deposited on both sides of the basement membrane leaving the membrane itself intact.[18] This could interfere with the function of the glomerular epithelium (podocytes) and lead to proteinuria. Ultimately, the glomerular capillaries become obstructed and nonfunctioning, leading

TABLE 1

Pathologic and Clinical Data on 15 Patients with Renal Amyloidosis

Case	Age	Sex	Clinical Classification	Associated Disease	Means of Diagnosis	Severity of Glomerular Disease	Type of Renal Disease	Urinary Protein	Alb./Glob. gm./100 ml.	Cholesterol, mg./100 ml.	Non-protein nitrogen, mg./100 ml.	CO_2-Combining power, mEq./L.	Serum Electrophoresis
1	25	M	Primary	Syphilis	Biopsy	Mild	Nephrotic syndrome	13 gm./day	2.4/1.9	344	28	27	Elevated alpha$_2$ globulin
					Biopsy	Mild	Remission	3+	5.1/1.8		12		
2	53	M	Primary		Biopsy	Moderate	Nephrotic syndrome	4+	2.2/1.2	907	22	24	Elevated beta globulin
3	56	M	Primary	Pyelonephritis	Autopsy	Moderate	Obstructive uropathy, uremia	4+	2.8/2.0		108	17	Elevated gamma globulin
4	56	F	Primary	Bronchopneumonia, old myocardial infarction	Autopsy	Mild	? Tubular acidosis	1+	3.3/3.5	116	46	18	
5	67	M	Myeloma	Myxedema	Autopsy	Marked	Uremia	3+	3.4/2.6	496	130	19	Normal
6	57	F	Secondary	Rheumatoid arthritis	Biopsy	Marked	Nephrotic syndrome	4 gm./day	1.9/2.5		32	27	
					Autopsy	Marked	Nephrotic syndrome, uremia	9 gm./day	1.9/1.3	284	168	10	
7	41	M	Secondary	Werner's syndrome, leg ulcers, old TB	Autopsy	Marked	Uremia	3+	3.9/2.2	703	108		
8	49	F	Secondary	Tuberculosis	Autopsy	Marked	Tubular acidosis, nephrotic syndrome	4+	1.9/4.5		43*	10	
9	69	M	Secondary	Rheumatoid arthritis, furunculosis	Biopsy	Moderate	Nephrotic syndrome	5 gm./day	2.5/2.9	326	41	31	Elevated alpha$_2$ globulin
10	76	F	Secondary	Rheumatoid arthritis	Congo red		Uremia	1+	3.6/2.0	220	102	15	
11	69	M	Secondary	Lung abscess	Autopsy	Moderate	Nephrotic syndrome	3+	1.9/3.8	350	51	28	
12	61	M	Secondary	Tuberculosis	Autopsy	Moderate	Nephrotic syndrome	4+	2.0/2.8	351	20*		
13	27	M	Secondary	Tuberculosis	Congo red		Nephrotic syndrome	14 gm./day	2.3/3.9	235	32	40	Elevated alpha$_2$ globulin
14	43	M	Secondary	Tuberculosis	Autopsy	Marked	Nephrotic syndrome	4+					
15	59	M	Secondary	Tuberculosis	Autopsy	Marked	Nephrotic syndrome	3+			23		

* Blood urea nitrogen (mg./100 ml.)

to renal insufficiency. Amyloid may also involve the larger arterioles, and less commonly the interstitial tissues and tubules, particularly in the medulla.

It has been previously suggested that the severity of acidosis is often out of proportion to the degree of nitrogen retention in renal amyloidosis.[19] In the present series, one patient with nephrotic syndrome and minimal azotemia had severe acidosis (case 8). Recently, renal tubular acidosis has been described in other forms of nephrotic syndrome.[20] One other patient had moderate acidosis with normal serum protein and urea levels (case 4). In the remaining patients, the relationship between the acidosis and azotemia was similar to that seen with other types of renal failure.

Rarely, local amyloid deposits may obstruct the urinary tract (case 3).[21, 22] As in case 3, obstruction may lead to hydronephrosis, pyelonephritis, and renal calculi.

Clinical remissions of the nephrotic syndrome due to amyloidosis are rare. Previously reported instances have all been the result of treatment of reversible diseases such as tuberculosis, chronic suppurative processes, myxedema, and rheumatoid arthritis.[11, 23-26] In case 1, we had the unique experience of observing a spontaneous clinical remission in a patient who had nephrotic syndrome apparently due to primary amyloidosis. A second biopsy specimen obtained during the remission showed little histologic change. Persistence of amyloidosis on renal biopsy during a clinical remission of the nephrotic syndrome has also been reported in a patient with quiescent rheumatoid arthritis.[11] However, in contrast to our case, this patient did show regression of hepatosplenomegaly. Resorption of amyloid deposits in the liver and spleen, with persistence of amyloid in the kidney, has been observed in animal experiments.[26] In this case, as in other forms of the nephrotic syndrome, it is necessary to distinguish between a clinical remission and an alteration of the basically progressive nature of the disease.

We have attempted to classify our patients as having primary amyloidosis, secondary amyloidosis, and amyloidosis occurring with multiple myeloma solely on the basis of the presence or absence of associated disease. However, even this simple classification often did not allow us to characterize our cases, or to predict consistent clinical or pathologic differences among the three groups. It was not possible to make a satisfactory separation of our cases into these three groups on the basis of distribution of amyloid or from its staining properties. Bearing in mind the difficulty in classification, it seems likely that amyloidosis was primary in five cases of the present series. This is an unusually high proportion compared with the average incidence of less than 4% found in seven large, published series.[27-33] In these general hospital series, published between 1933 and 1955, amyloidosis secondary to tuberculosis and other chronic infections accounted for over 80% of the cases. Since severe and protracted infections which may cause secondary amyloidosis are now being treated more successfully, it is not surprising that the relative incidence of other forms of amyloidosis should also increase.

Primary amyloidosis and the amyloidosis associated with multiple myeloma have many features in common. Indeed, it has been suggested that they are varieties of the same disease.[34, 35] Some of the interrelationships between the manifestations of amyloidosis and multiple myeloma are illustrated by cases 2, 3, and 5 of the present series. Case 2, as well as numerous previously reported cases of primary amyloidosis,[35–38] had an increased number of plasma cells in the bone marrow. The serum electrophoresis of case 3 showed a sharp peak with the mobility of gamma globulin which was considered typical of "myeloma" protein. A similar pattern was recently reported in a patient with generalized amyloid infiltration and accumulations of lymphocytes in many tissues.[39] However, our case 3 showed no abnormalities of the hematopoietic system at post-mortem.

Nephrotic syndrome has not been reported in patients with amyloidosis associated with multiple myeloma, in contrast to its frequent occurrence in patients with primary amyloidosis. Proteinuria and renal failure are frequent in multiple myeloma, but these are seldom due to amyloidosis.[35, 40, 41] Characteristically, renal amyloidosis associated with multiple myeloma shows vascular infiltration with little glomerular involvement. We were able to find only one case reported to have marked amyloid infiltration of the glomeruli at post-mortem, such as seen in our case 5.[40] However, case 5 also had myxedema which can cause secondary amyloidosis with glomerular involvement.[24] In these cases, renal amyloidosis can be reversed by administration of thyroid.[42]

Although reports in the literature conflict, it is likely that corticosteroids are of no value in the treatment of amyloidosis.[11, 42–46] Patients with nephrotic syndrome and amyloidosis have not shown diminished albuminuria or diuresis on steroid therapy (cases 2 and 6).[37, 47, 48] Furthermore, three years of corticosteroid therapy for rheumatoid arthritis did not prevent the appearance of amyloidosis in case 6.

The possibility that amyloidosis can be associated with a hereditary disorder such as Werner's syndrome is suggested by case 7. Moreover, in the two previously reported autopsied cases of Werner's syndrome, "hyalinized connective tissue" was found in the glomeruli and arterioles.[49, 50] Amyloid deposits could be mistaken for hyalinized connective tissue with ordinary stains and in these reports the use of special stains for amyloid is not recorded.

There is no explanation for the variable sites of predilection for amyloid deposition. Our experience with cases 3, 4, and 5 raises the possibility that an organ is particularly prone to amyloid infiltration if it has been the site of a pre-existing disease or injury.

As previously noted, it was difficult in an individual case to differentiate between primary and secondary amyloidosis (cases 1, 4, and 7) or between these types and the amyloidosis associated with myeloma (cases 2, 3, and 5). This difficulty could indicate that amyloidosis is actually a single disease,

or, more likely, that there is a common etiologic factor for all three types. There is evidence to suggest that this factor may be a disturbance of protein metabolism. The amyloid deposit itself is glycoprotein in nature [51, 52] and the disorder can be reproduced in experimental animals by feeding them protein.[26, 42, 46, 53] The list of diseases which may lead to secondary amyloidosis in man is extremely long.[19, 24, 27-33, 43, 54] Most of these diseases are characterized by prolonged stimulation of the immune response with plasmacytosis and hyperglobulinemia. Serum electrophoresis in both primary and secondary amyloidosis frequently shows elevation of the alpha$_2$ globulin, as in cases 1, 8, and 13 in the present series,[12, 44, 51] the beta globulin as in case 2,[45, 55] or both.[11, 37] Electrophoretic abnormalities have also been found in asymptomatic members of a family with a high incidence of primary amyloidosis.[7] Similar electrophoretic abnormalities have been observed in casein induced amyloidosis in animals.[56, 57] It is possible that an immune response may be directly involved in the development of the amyloid lesion. Using the fluorescent antibody technic, large quantities of gamma globulin have been found in amyloid deposits.[58, 59]

Summary

Of 17 cases of amyloidosis seen at this center between 1954 and 1960, 15 had renal involvement. The kidneys were affected in four of five patients with primary amyloidosis. The characteristic clinical manifestation was the nephrotic syndrome. In four cases in this series, the diagnosis was established by renal biopsy. In one patient, there was a clinical remission of the nephrotic syndrome apparently due to primary amyloidosis. Some other unusual features of renal amyloidosis are discussed.

Acknowledgment

The authors wish to express their gratitude to Dr. David B. Jones for his invaluable assistance in reviewing the pathology.

Summario In Interlingua

In le serie de 17 casos de amyloidosis vidite a iste centro inter 1954 e 1960, 15 habeva affection renal. Dece de nostre patientes habeva le syndrome nephrotic. Biopsia renal esseva multo utile in iste casos. Il esseva solmente le prova histologic de amyloidosis que permitteva a nos distinguer definitemente iste casos ab alteres in que le syndrome nephrotic esseva le resultato de altere morbos. Tamen, per contrasto con certe altere occlusive morbos glomerular, il occurre nulle declino del proteinuria durante que le amyloidosis renal progrede verso uremia. In duo del 17 casos, acidosis esseva presente in coexistentia con normal o solo levemente elevate nivellos del urea del sanguine. Un de nostre patientes con amyloidosis primari experientiava un remission spontanee de su syndrome nephrotic sin ulle apparente alteration in le biopsias renal obtenite ante e post le remission. Le differentiation inter amyloidosis primari, amyloidosis secundari, e le amyloidosis que occurre con myeloma multiple poteva esser facite solmente super le base del constatation del presentia o absentia de morbo associate. In plure casos, un separation satisfacente de nostre casos non poteva esser facite mesmo super le base de iste simple definition. Nostre experientia con

tres de nostre patientes subleva le possibilitate que un organo es particularmente susceptibile de experientiar infiltration amyloide si illo ha previemente essite le objecto de morbo o trauma. Es discutite le evidentia in supporto de un rolo etiologic de anormalitates de proteina e de mechanismos immunologic.

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THE CONCENTRATION OF ANTIHEMOPHILIC GLOBULIN (AHG) IN PATIENTS WITH CORONARY ARTERY DISEASE *

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Blood coagulation bears an important relationship to atherosclerosis, first, because thrombosis is its most serious complication, and second, because one of the current theories of the pathogenesis of atherosclerosis is that the vascular lesions are initiated by mural thrombi. In both, a hypercoagulable state has been implicated as being responsible for the thrombosis.[1, 2]

Because of increasing understanding of the mechanism of blood coagulation, and newer technics, it is now possible to determine quantitatively the concentration of many clotting factors. It is felt that such factors, which are normally concerned with hemostasis, may be important in thrombus formation when present in increased concentrations.[3, 4]

This report presents data which indicate that there is an increased concentration of antihemophilic globulin (AHG) in patients who have had recent or remote myocardial infarction, compared with controls of comparable age. It is proposed that this represents a hypercoagulable state and that it contributes to the increased tendency to thrombosis in patients with coronary artery disease.

Materials and Methods

The patients with recent or remote myocardial infarction consisted of 59 individuals selected from the wards or the outpatient department. There were 51 males and eight females. Their ages ranged from 38 to 82 years. The control series of 43 cases, ranging in age from 38 to 78 years, consisted of hospital personnel or patients not suffering from any hemorrhagic disorder or from previous myocardial infarction. Of these, 29 were males and 14 were females.

Blood was collected by the two-syringe technic. The needles and syringes were siliconized with Dri Film Sc-87.† The blood withdrawn in the first syringe was discarded and a second siliconized syringe was attached to the needle to aspirate the blood used for testing. Nine milliliters of blood were transferred to a siliconized centrifuge tube containing 1 ml. of 3.5%

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† General Electric Co.

sodium citrate solution for AHG determination, or 0.1 molar potassium oxalate solution for thromboplastin generation test, and mixed. This was centrifuged at 3,000 rpm for 20 minutes, after which the plasma was separated and kept in ice water until used.

The thromboplastin generation test was performed by the method of Biggs and Douglas.[5] Blood from patients with myocardial infarction who were receiving anticoagulants (phenindione or bishydroxycoumarin) and blood from one of the controls was used to study the influence of plasma and serum factors on thromboplastin generation. After the thromboplastin generation test was performed on the blood of the patient and of the control, the patient's plasma was substituted for the control plasma and the thromboplastin generation test was repeated. Similarly, the patient's serum was substituted for the control serum and again the thromboplastin generation test was repeated.

Factor V activity was determined by measuring the corrective effect on the prothrombin time of aged plasma. Prothrombin time determinations for the control of anticoagulant therapy were performed by the method of Quick.[6] Antihemophilic globulin concentrations were determined by a modification of the method of Pitney.[7]

Results

The thromboplastin generation tests described above were performed in preliminary studies. In 12 of 16 patients with recent myocardial infarction the plasma appeared to possess increased thromboplastin activity as compared with controls. This is illustrated in Figure 1, curves I and III. It is well known that patients receiving oral anticoagulants develop impaired thromboplastin generation due to a deficiency of one or more serum factors,[8, 9] as seen in Figure 1, curves III and IV. Nevertheless, the increased thromboplastin activity of the patient's plasma can be readily seen in the difference between curves III and IV, as well as in the difference between curves I and II.

Simultaneous determination of Factor V concentration revealed no significant change from the normal. As barium sulfate-adsorbed plasma contains both Factor V and AHG (antihemophilic globulin, Factor VIII), the results suggested that the increased thromboplastin generation may be due to an increased concentration of AHG. This was confirmed by specific determination of AHG. As a result of these preliminary findings, the concentration of AHG was determined in a series of patients and controls of comparable age.

Previous work revealed that the AHG concentration in controls, ranging in age from 17 to 78 years, showed a progressive increase with aging which was most marked in those over 40.[7] However, patients with coronary artery disease, as represented by recent or remote myocardial infarction, had an even higher concentration than did controls of comparable age. This is

readily visualized in Figure 2, where the mean values for groups are plotted. Although the mean values reveal significant differences, there was considerable overlapping in individual determinations between the two groups.

Although most patients were studied during the acute phase of their myocardial infarction, nine cases were investigated from two months to two

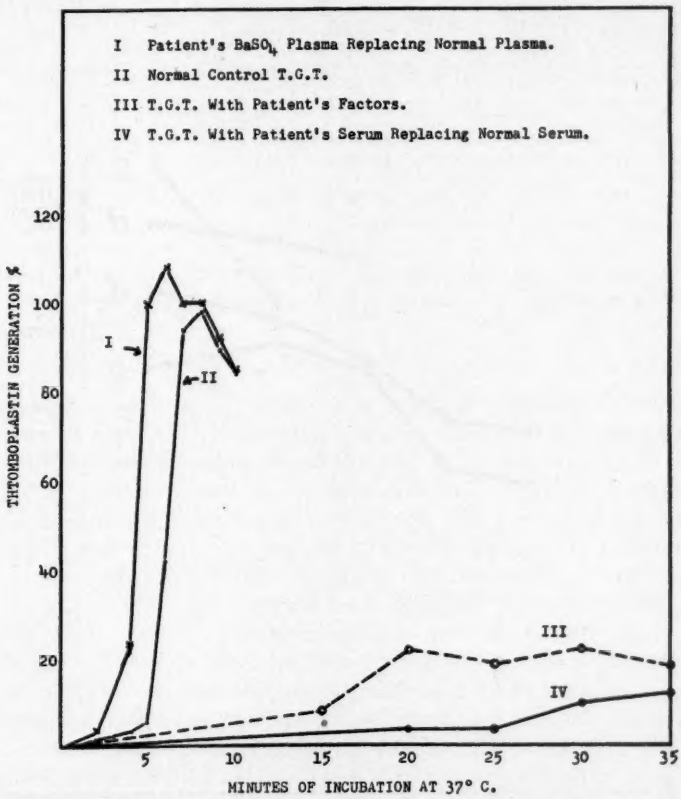

FIG. 1. Thromboplastin generation test of a patient with acute myocardial infarction receiving phenindione (curve III), and a control (curve II). It can be seen that with the patient's plasma (curves I and III) more thromboplastin is generated than with control plasma (curves II and IV).

years after they had suffered their infarction. They had AHG concentrations of 195, 162, 153, 152, 143, 140, 138, 122, and 118%, with a mean of 147%. These results would indicate that the high concentrations of AHG in coronary artery disease have no relation to the acute illness, nor are they directly related to the myocardial necrosis. Actually, a fall in AHG has been reported following tissue injury.[10]

Most patients were receiving oral anticoagulants during these studies. Investigations before and during anticoagulant therapy in six patients revealed a mean AHG concentration of 143% before anticoagulants were begun and a mean of 153% in from three to 12 days after starting anti-

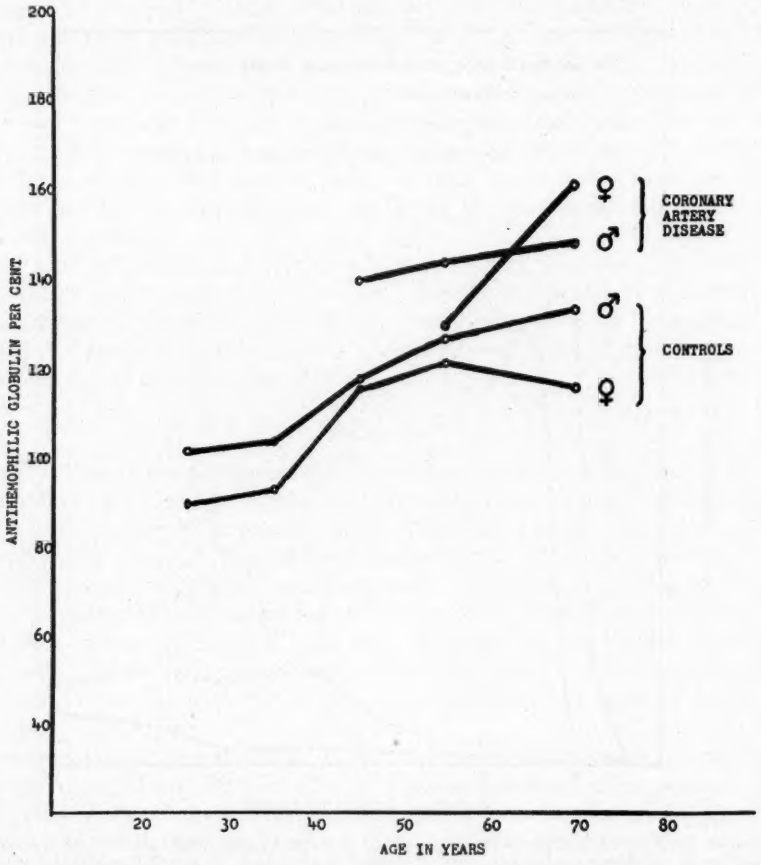

FIG. 2. Mean AHG concentrations in controls and in patients with coronary artery disease grouped according to age and sex.

coagulants. Hence it was concluded that anticoagulants did not significantly alter the results.

Because of the disproportionate number of patients and controls in each age group, and because of the small number of females with coronary artery disease, the data were subjected to an analysis of variance for disproportionate subgroups between male patients and male controls only.[11] This

TABLE 1

AHG Concentrations in Patients with Coronary Artery Disease and in Controls of Comparable Age

Group	Age Group	Coronary Artery Disease			Controls			Analysis of Variance
		No.	Mean Conc. AHG%	Stand. Error $\sqrt{\frac{849.21}{N}}$	No.	Mean Conc. AHG%	Stand. Error $\sqrt{\frac{849.21}{N}}$	
I	38–49	11	139	8.78	9	117	9.71	
II	50–59	21	143	6.36	11	126	8.78	$p<0.025$
III	60–80	19	147	6.68	9	132	9.71	
Total	38–80	51	143	4.08	29	125	5.41	

revealed that the difference in AHG concentration between the coronary artery disease group and the controls was statistically significant (Table 1).

DISCUSSION

Although atherosclerosis is the basic defect in coronary artery disease, thrombosis is its most serious complication. Considerable evidence points to the fact that the pathogenesis of thrombosis in coronary artery disease may not be directly related to the atherosclerosis.[1] Owren [12] emphasized that the incidence of coronary atherosclerosis has not increased since the beginning of the century, whereas the number of myocardial infarctions has risen considerably. Yudkin,[13] discussing the epidemiology of coronary disease, states: "We must conclude that, whatever the factors which cause atheroma, they are not entirely coincident with the factors which cause thrombosis." This was based on the evidence that certain populations with a low incidence of coronary thrombosis, such as those in Italy and Japan, do not necessarily have a low incidence of atheroma. In cases of sudden death from coronary thrombosis, Duguid [2] has frequently noted the presence of thrombi in other vessels as well, and this has suggested to him "some thrombogenic influence more powerful and generalized than mere local damage to the vessel wall." The general implication appears to be that a hypercoagulable state may be responsible for thrombosis in coronary artery disease.

Hypercoagulability of the blood implies evidence of increased concentration of one or more clotting factors. Blood coagulation, as we know it at present, is a complex process involving many factors which are grouped according to their role in the various stages of the clotting mechanism. Thus thromboplastin formation is dependent on the activation of PTA (plasma thromboplastin antecedent), AHG (antihemophilic globulin), PTC (plasma thromboplastin component), Stuart-Prower factor, Factor V, cal-

cium, and platelets. Thrombin formation requires prothrombin, Factor VII, Factor V, Stuart-Prower factor, calcium, and thromboplastin. Fibrinogen is finally converted to fibrin in the presence of thrombin. Although the Hageman factor appears to be the glass activating factor and is important in the initiation of clotting in glass tubes, its role in vivo is uncertain, as no serious compromise of the hemostatic mechanism occurs in its absence.

In a hypocoagulable state, bleeding, despite its frequently diffuse nature, usually occurs at sites related to local vascular disturbance. Similarly, in a hypercoagulable state, thrombosis results at sites of local vascular disease. It appears likely that, whereas a reduction of a clotting factor in the

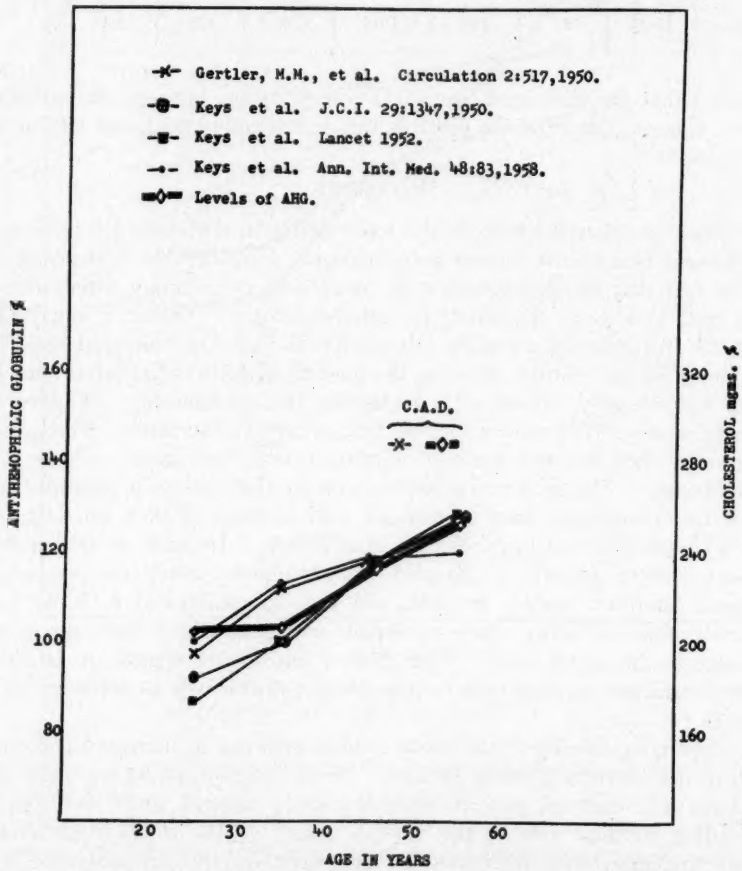

FIG. 3. Parallel relationship between AHG concentration and cholesterol levels in male controls (lower curves) and in patients with coronary artery disease (upper single mean concentrations).

later stages of blood coagulation may result in bleeding, an excess of the same factor may be unimportant in the pathogenesis of thrombosis. Initiation of the clotting process is dependent on thromboplastin formation, which in turn affects the factors concerned in the later stages. Thus, an increase of a clotting factor required in the initial stages of blood coagulation would play a much greater role in the pathogenesis of thrombosis. Although the sequence of events in the initiation of the clotting process is not completely clarified, activation of PTA, PTC (plasma thromboplastin component), and AHG appears to be the earliest step, and precedes the reaction with platelets in thromboplastin production.[4, 14] Thus, an increase of one or more of these factors predisposes to an increased rate and amount of thromboplastin produced. Our findings would indicate that an increased concentration of AHG would then predispose to increased thromboplastin formation and thrombosis in patients with coronary artery disease.

Indirect evidence of an increased concentration of AHG has been presented by McDonald and Edgill.[15] They demonstrated an increased generation of thromboplastin in patients with ischemic heart disease. Similarly, Mustard [16] found that the plasma of patients with atherosclerotic vascular disease possessed increased thromboplastin activity as compared with controls. He also obtained increased concentrations of PTC in these cases.

Our demonstration of an increased concentration of AHG with aging,[7] and of an even greater concentration in patients with coronary artery disease, parallels the findings of others with regard to cholesterol levels [17] (Figure 3).

If one can conclude that cholesterol is important in the pathogenesis of atherosclerosis, a similar conclusion may be reached with regard to AHG. This would lend support to Duguid's views regarding the thrombotic etiology of atherosclerosis.[2] This, however, is not borne out by events in patients with hemophilia, who have negligible amounts of AHG in their blood. One of our patients with hemophilia, who died at age 53, had a moderate degree of generalized arteriosclerosis which included the coronary arteries and the aorta. In addition, a case of severe angina in a patient with hemophilia, revealing marked atheromatous and calcified vessels on postmortem, was recently reported.[18] Thrombosis was absent in both cases. Thus, AHG would not appear to play an etiologic role in atherosclerosis. Whether the increased concentrations of AHG are consequent to the development of atherosclerosis or unrelated remains to be determined. It does not, however, detract from its possible role in the pathogenesis of thrombosis in patients with atherosclerosis.

Summary and Conclusions

1. Evidence has been presented that patients with coronary artery disease, as manifested by recent or remote myocardial infarction, possess an increased concentration of antihemophilic globulin, compared with controls of comparable age.

2. It is suggested that the increase in antihemophilic globulin represents a hypercoagulable state and may predispose to thrombosis in patients with coronary artery disease.

Summario In Interlingua

Le coagulation del sanguine es significativemente relationate con atherosclerose, primo: proque thrombose es le plus serie complication de atherosclerose, e secundo: proque un del currente theorias in re le pathogenese de atherosclerose assere que le lesiones vascular es initate per thrombos mural. In ambe iste situationes, un stato de hypercoagulabilitate es considerate como responsabile pro le thrombose.

Cinquanta-novem patientes con recente o distante infarcimento myocardial esseva studiate. Le serie includeva 51 masculos e octo femininas, con etates de inter 38 e 82 annos. Esseva usate 43 subjectos de controlo, de comparabile etates.

Tests de generation de thromboplastina esseva executate initialmente. Esseva constatate un plus grande generation de thromboplastina in patientes con morbo de arteria coronari que in le subjectos de controlo. Le factor responsabile pro iste augmento esseva trovate in le fraction in le plasma. Esseva demonstrate que illo resulta de un plus forte concentration de globulina antihemophilic (GAH).

Determinationes specific de GAH in iste serie de patientes e subjectos de controlo revelava un plus grande concentration de GAH in le patientes con morbo de arteria coronari que in le subjectos de controlo. Le differentia esseva statisticamente significative.

GAH es un factor importante in le stadios initial del coagulation del sanguine e le formation de thromboplastina. Es opinate que un factor con iste typo de activitate es plus significative ab le puncto de vista del pathogenese de thrombosis que factores que participa plus tarde in le mechanismo coagulatori e depende de un activation per thromboplastina.

Un corpus considerabile de datos ab studios clinic, pathologic, e epidemiologic suggere que le pathogenese de thrombose coronari es sin relation con atherosclerose. In un stato de hypercoagulabilitate, le occurrentia de thrombosis es plus probabile in un sito de local morbo vascular—per exemplo in un placa atheromatose—que in un vaso normal.

Nostre constatation del existentia de un augmentate concentration de GAH in patientes con morbo de arteria coronari suggere que isto representa un stato de hypercoagulabilitate e un predisposition pro-thrombotic.

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ESOPHAGITIS ASSOCIATED WITH HEMORRHAGE FROM ESOPHAGEAL VARICES *

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The mechanisms which operate to produce hemorrhage from esophageal varices are not entirely clear. It has been suggested that esophagitis may be a factor contributing to the eventual rupture of varices in the esophagus.[1, 2] In order to investigate this hypothesis we have reviewed the endoscopic findings in 120 patients with esophageal varices, of whom 71 had a history of hemorrhage.

Methods

One hundred twenty patients representing successive cases of esophageal varices diagnosed by esophagoscopy were included in this study. Almost without exception, the primary disease in these patients was hepatic cirrhosis. Esophagoscopy was performed to investigate the cause of gastrointestinal hemorrhage, or as a part of the physical examination of a patient known to have cirrhosis. In no instance did the examination have any deleterious effect upon the patient, even though many of the examinations were made during or immediately after an episode of massive bleeding from varices.

The esophagitis noted in these cases was of a superficial type characterized by moderate to marked hyperemia of the mucosa in association with edema, granularity, and the presence of an inflammatory exudate. For the purposes of this study a diagnosis of esophagitis was not made if esophageal tamponade with a Sengstaken-Blakemore tube had been employed within the two weeks before esophagoscopy.

Results

Forty-four patients were examined within 14 days of a bleeding episode. Twenty-one (46%) had definite evidence of esophagitis. This lesion was seen in only 12 (15%) of the 76 patients with varices who had not had recent hemorrhage (Table 1).

Three of the 12 patients with esophagitis who had not had recent bleeding had a documented history of hemorrhage. Table 2 summarizes the incidence of esophagitis found in patients who have had a documented history of hemorrhage at any time. The implication of such an analysis is that the esophagitis is constantly present once it appears. This may not, in fact,

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TABLE 1

Esophagitis Associated with Recent Variceal Hemorrhage

	Varices	Varices & Esophagitis	%
No recent hemorrhage	76	12	15
Recent hemorrhage	44	21	46
Totals	120	33	

be true, but rather inflammation may well occur only intermittently. Such a situation was evident in a few patients whom we examined repeatedly over a two to three-year period; others, however, demonstrated inflammation consistently. This information is tabulated in an effort to include more patients with hemorrhage in the analysis.

TABLE 2

Incidence of Hemorrhage at Any Time and Esophagitis in 120 Patients with Varices

	No. of Patients	%
Hemorrhage	71	
Esophagitis	24	34
No Hemorrhage	49	
Esophagitis	9	19

Nine of the 120 patients had hiatus hernia associated with varices. Eight of these patients had histories of repeated hemorrhage. Seven of the eight patients were examined shortly after hemorrhage and four were found to have had esophagitis while three had no inflammation. The one patient who has never hemorrhaged has been found to have had esophagitis on one occasion but was free of such inflammation on examinations prior to and subsequent to that examination.

Analysis of the nine patients with esophagitis who had never bled revealed that six of these cases had marked ascites. The coincidence of these two conditions in the entire group of 120 patients was therefore reviewed. Twenty-three patients were found who presented with marked ascites. Thirteen of these cases had esophagitis when examined and seven had bled. Table 3 summarizes this information.

DISCUSSION

Evidence implicating esophagitis with ulceration as a responsible factor in hemorrhage from varices has been adduced by several investigators who

TABLE 3

Esophagitis and Hemorrhage in 23 Patients with Ascites

	No. of Patients
No Hemorrhage	13
Esophagitis	6
Hemorrhage	10
Esophagitis	7

examined autopsy material from patients who died of variceal hemorrhage. Wagenknecht [1] and co-workers reviewed the gross and microscopic morphology of 44 such cases and concluded that 43% had ulcerative lesions overlying varices that were responsible for hemorrhage and which they presumed were due to acid gastric regurgitation. They described the lesions as multiple small areas of ulceration, visible in many cases only microscopically, and consisting of breaks in the mucosa surrounded by an inflammatory reaction. Chiles et al.[2] carried out a similar study in 80 instances of fatal varix hemorrhage and found that 45 patients (56%) had erosions overlying a varix. They concluded, however, that the significance of such findings was questionable in light of the frequency with which ulcerative lesions are generally found at necropsy. The present analysis indicates a high incidence of inflammation of the esophageal mucosa in patients who have recently bled from varices. Because of the difficulties in assessing the significance of inflammatory lesions seen at necropsy, inflammation of the esophagus observed during esophagoscopy in patients with varices provides more convincing evidence that such a factor exists in the pathogenesis of hemorrhage from varices. The coincidence of esophagitis and varices at esophagoscopy has been noted by other observers. Palmer [3] in reviewing 100 patients with subacute erosive esophagitis stated that he found 14 with varices coincident with esophagitis, each of whom had a history of hematemesis. Furthermore, McGlone [4] stated that he had seen peptic esophagitis during endoscopy in perhaps 10 to 20% of patients who had varices.

The observation that repeated hemorrhage frequently occurred in patients with varices and hiatus hernia supports the presumption that reflux of gastric contents with resultant esophageal inflammation is a factor in precipitating varix hemorrhage since reflux is a frequent accompaniment of hiatus hernia. The frequency with which esophageal inflammation occurred in patients with ascites is probably explained by the fact that increased intra-abdominal pressure alters normal subdiaphragmatic relationships, rendering the cardiac mechanism less efficient. The integrity of the esophagogastric junction is not solely dependent upon an intrinsic mechanism, but anatomic relationships in the immediate vicinity are in part responsible for maintaining the integrity of the gastroesophageal closing mechanism.[5] It is probable that change in liver size in either direction also interferes with the usual relationships around the esophagus which ordinarily helps prevent reflux.

The incidence (46%) of inflammation in association with recent variceal hemorrhage noted in this study is in agreement with the incidence of ulceration found in necropsy material by Wagenknecht (43%) and Chiles (56%) and serves to strengthen the premise that in some cases esophagitis is an important factor in producing hemorrhage. Finally, 20% of our patients with varices had superficial inflammation but had never bled, emphasizing the fact that a combination of factors having different multiples in individual

cases is necessary to complete the unknown portion of the equation which eventually equals the catastrophe of hemorrhage from varices.

Summary

1. Superficial esophagitis is present in approximately 40% of patients with recent hemorrhage from varices.

2. Patients with esophageal varices and hiatus hernia have an extremely high incidence of recurrent variceal hemorrhage.

3. Disturbance of subdiaphragmatic anatomic relationship as a result of ascites, or change in liver size is considered to be a mechanism for allowing gastric regurgitation with subsequent esophageal inflammation.

4. It is suggested that esophagitis is a contributing factor to hemorrhage from esophageal varices.

Summario In Interlingua

Esseva revistate le constationes esophagoscopic in 120 patientes con varices esophagee pro determinar le incidentia de esophagitis in le presentia de hemorrhagia ab varices. Quaranta-sex pro cento del patientes examinate intra duo septimanas post hemorrhagia (e qui non habeva habite tamponage esophagee) revelava evidentia de esophagitis. Iste lesion esseva vidite in solmente 15% del patientes qui non habeva habite un hemorrhagia recente. Novem del 120 patientes habeva hernia hiatic associate con varices e octo de istes habeva habite repetite hemorrhagias. Vinti-tres del patientes examinate habeva marcate grados de ascites, e in 13 de istes le presentia de esophagitis esseva constatate quando illes esseva examinate. Solmente septe del 13 habeva habite un sanguination anteriormente.

Le incidentia (46%) de inflammation coexistente con recente hemorrhagia ab varices esophagee es strictemente de accordo con le incidentia notate per altere autores qui examinava materiales necroptic pro evidentia de ulceration in le presentia de hemorrhagia ab varices.

Le alte incidentia de repetite hemorrhagia in patientes con coexistente hernia hiatic e varices esophagee supporta le supposition que refluxo gastric es un factor in precipitar inflammation e hemorrhagia, viste que illo es un frequente accompaniamento de hernia hiatic. Augmento del pression intra-abdominal ab ascites contribue possibilemente al occurrentia de refluxo gastric, con le production de inflammation esophagee. Alterationes del dimensiones hepatic es etiam possibilemente capace a afficer le relationes anatomic in le ambiente del cardia e facilitar le refluxo con resultante inflammation. Le absentia de hemorrhagia in certe patientes con varices e esophagitis sublinea le importantia de incognite factores in le production de hemorrhagia ab varices.

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LUNG CANCER AMONG INDIANS OF THE SOUTHWESTERN UNITED STATES *

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DESPITE widespread opinion that American Indians seldom develop malignancy, there is little precise information in this regard. The present report concerns a study of the occurrence of lung cancer among Indians of the southwestern United States. Data on malignancy discovered in other parts of the body have been included for comparative purposes.

METHODS AND MATERIALS

One of the authors (S.L.C.) interpreted all chest x-ray films for the Phoenix Public Health Service Indian Hospital and for most of the area field units from 1954 to 1960. Information derived from this experience afforded the primary basis for this study.

The Phoenix P.H.S. Indian Hospital serves as a referral center for nine field hospitals and seven field clinics located on the numerous Indian reservations in Arizona, Nevada, California, and Utah. Indians residing in the vicinity of Phoenix or on nearby reservations are also admitted to this general hospital. Some 44 different tribes are represented among the patients studied, the vast majority of them from the Pima, Apache, Papago, Hopi, Supai, Hualapai, Yavapai, Mojave, Maricopa, and Navajo tribes. In 1960 the estimated Indian population of reservations served by the Phoenix area hospitals and field clinics was 76,310.[1]

All pertinent available hospital records were studied for the period 1954 through 1960 (fiscal years). Material examined included diagnostic files, medical records, autopsy reports, death certificates, surgical pathologic files, hospital cancer registry and x-ray files. The death certificate and autopsy information is based on 234 adult deaths with 153 autopsy examinations (65.4%).

RESULTS

During the seven-year period 1954 through 1960 (fiscal years), 12,511 patients (8,287 adults) were admitted to the Phoenix P.H.S. Indian Hospital from an estimated population of 76,310 Indians. Although informa-

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tion on sex distribution is incomplete, it is estimated that there were slightly fewer adult male than female admissions. Comparative statistics regarding malignancy of various sites in the study group of Indians are shown in Table 1.

The information especially pertinent to this investigation is the singular absence of lung cancer. Gastric malignancy, on the other hand, was discovered in 13 Indians. Among Caucasians of the United States the incidence of cancer of the lung and stomach are similar.[2]

During the seven-year study period, more than 50,000 chest x-ray films * of Indians were examined by one of the authors (S.L.C.), without any primary pulmonary malignancy being detected. Indian inpatients and out-

TABLE 1

Number of Cases of Malignancy Discovered Among Southwest American Indians (12,511 Hospital Admissions) by Site, 1954–1960*

Site	Number of Cases
Stomach	13
Colon	4
Gall-bladder and biliary tract	8
Liver	4
Pancreas	6
Breast	5
Uterus	10
Ovary	4
Prostate	6
Kidney	3
Penis and testicle	1
Skin	4
Bone	3
Thyroid	5
Salivary gland	1
Brain	1
Unknown site	4
Lymph node†	5
Scalene node (metastasis)	0
Lung	0

* Although the figures presented are for the 12,511 hospitalized individuals, they have been selected from the total southwestern Indian population of an estimated 76,310.

† Refers to such conditions as Hodgkin's disease or leukemia.

patients at the Phoenix P.H.S. Indian Hospital, nine field hospitals, and seven field clinics are included among the chest x-ray examinations. Although lung cancer was suggested in the chest x-ray examinations of two patients, subsequent clinical studies established the pulmonary lesions to be metastatic.

DISCUSSION

In the death certificate study of Smith et al.,[3] it was concluded that the Navajo, in comparison with the general population, experience a deficit of cancer in general and, specifically, of cancer of the breast, prostate gland,

* Actually, complete data on enumeration are available for only three years, 1957 through 1959; during this time 15,686 chest films were interpreted for the Phoenix P.H.S. Indian Hospital and an estimated similar number interpreted for field units.

and lung. Similarly, Kraus [4] reported from his investigation of all the Indian tribes of Arizona, exclusive of Navajo, that there was significantly less morbidity and mortality from cancer in Indians than in Caucasians. This finding existed for each age group, so that the lower life expectancy of Indians did not explain the discrepancy. No attempt has been made in the present investigation to compare the occurrence of malignancy of various types in Indians and in Caucasians. However, the striking absence of lung cancer in this large segment of Indian population is in extreme contrast to the situation in the white race, whose death rate from this condition is reported as 16.6 per 100,000 among nonsmokers and 158.8 per 100,000 for smokers over the age of 55 years.[5]

Either hereditary or environmental factors may be related to the apparent marked deficit of lung cancer among Indians of the southwestern United States as found in the present study. It is likely that Indians residing on reservations have little exposure to the environmental factors which are suggested to have a possible relationship to the development of pulmonary malignancy. There is apparently very little contamination of the air by industrial fumes on the isolated reservations. In addition, cigarette smoking is much less frequent among the Indian study group than among Caucasians, and Indians who do use cigarettes seldom do so to the extent common in the white population. Precise data on environmental conditions are not available, but further investigation of anything which may be related to the apparent decreased occurrence of lung cancer among Indians of the southwestern United States seems indicated.

Summary

A striking absence of lung cancer was found among Indians of southwestern United States in a seven-year hospital study. It is not known whether hereditary or environmental factors are related to this deficit. However, minimal exposure to industrial fumes and infrequent use of cigarettes among the Indian population may be noteworthy findings. Further investigation is required to determine the conditions of significance in the deficiency of lung cancer among Indians of this area.

Summario in Interlingua

Le occurrentia de cancere pulmonar inter indianos del sud-west del Statos Unite esseva evalutate in un septenne studio de radiogrammas thoracic e de varie notationes hospitalari. Un diagnose de malignitate pulmonar non esseva establite in ulle del indianos, ben que cancere gastric esseva trovate in 13. Americanos de racia blanc ha simile incidentias pro cancere pulmonar e pro cancere gastric. Factores de hereditate o de ambiente debe esser responsabile pro iste marcate deficit de malignitate pulmonar in le indianos del sud-west. Il merita possibilemente esser signalate que le isolate terrenos reservate del indianos suffre un exposition minimal a vapores industrial e que le indianos studiate es infrequente usatores de cigarrettas.

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GLUCOSE AND CORTISONE–GLUCOSE TOLERANCE IN NORMAL AND "PREDIABETIC" HUMANS *

By Thomas H. Lambert, M.D., F.A.C.P., Roy B. Johnson, M.A., and Geoffrey R. Paul, M.D.,† *La Jolla, California*

Detection of the potential diabetic is a principal objective of clinicians and many investigators. The classical work of Fajans and Conn [1–4] and the investigations of West [5, 6] have focused attention on the use of cortisone in diagnosis and prediction of diabetes mellitus.

The purpose of the present study was to investigate and to evaluate both glucose tolerance and cortisone-glucose tolerance in otherwise normal individuals and in subjects with a hereditary background for diabetes.

Subjects and Procedures

Three hundred active subjects including controls, diabetics, and relatives of diabetics were studied. The diabetic relatives were blood-related kin of known diabetics and were not limited solely to a direct lineage group. Each patient received a maintenance diet containing at least 300 gm. of carbohydrate daily for three days preceding standard and cortisone-glucose tolerance tests, which were performed according to the method of Fajans and Conn. The glucose load used was 1.75 gm. of glucose per kilogram of ideal body weight. For the cortisone-glucose tolerance test 50 mg. of cortisone acetate was administered orally eight and one-half hours and again two hours before a standard glucose tolerance test. If body weight exceeded 160 pounds the doses of cortisone were 62.5 mg. Simultaneous capillary and venous blood glucose levels taken while fasting and at half-hour and one-hour intervals for three hours were determined by a modified Somogyi-Nelson technic.

Criteria for our interpretation of normal glucose tolerance and cortisone-glucose tolerance were established from the statistical treatment of data obtained from normal patients who had no diabetic relatives. The case histories of these subjects were carefully reviewed in search of the various factors that might affect carbohydrate tolerance. In the statistical analysis of data two and three standard deviations from the mean were considered

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to be significant, and this plan was used in establishing levels for normal standard and cortisone-glucose tolerance tests.

The data reported herein are derived from individuals having an ideal weight range as set by the tables of the Metropolitan Life Insurance Company of New York. The control group included 40 males (ages 12 to 64, mean 45 years) and 30 females (ages 22 to 76, mean 45 years). In the group having diabetic relatives were 36 males (ages 10 to 70, mean 42 years), and 38 females (ages 11 to 67, mean 42 years).

Data obtained from the known diabetic, obese, and other disease groups are not included in this report.

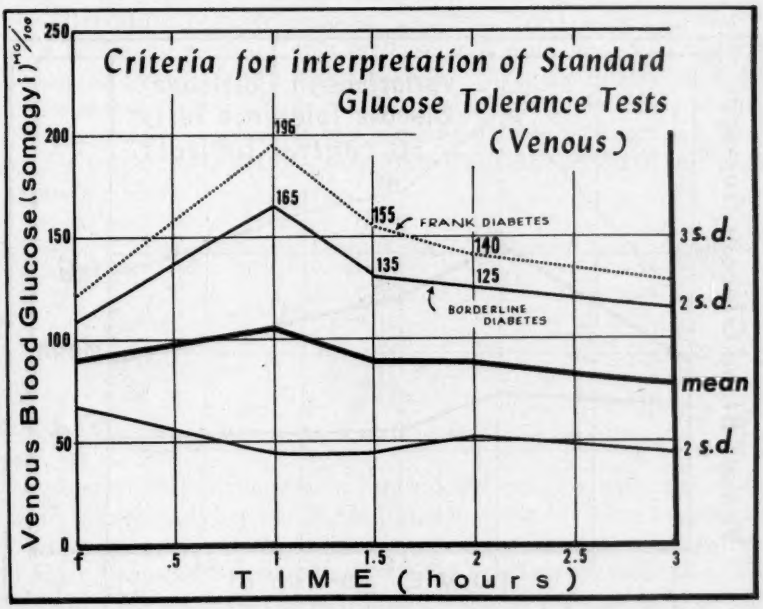

FIG. 1. Range of glucose tolerance after statistical treatment of results in 70 control subjects.

RESULTS

Standard Glucose Tolerance Tests: In Figure 1 are shown our criteria for interpretation of the standard glucose tolerance test from the results obtained in the 70 control subjects who had no family history of diabetes. The mean age of the group is 45 years. Venous glucose values taken while fasting, at one hour, one and one-half hours, two hours, and three hours are expressed as "true" blood sugar levels. These results are accompanied by the range of values encompassed by three standard deviations, and because of the statistical premise that 99% of the normal population would have values

for blood sugar within this range, those patients whose glucose levels exceeded two standard deviations were classified as a borderline group. A definitely abnormal category of frank diabetes was considered when blood sugar levels were above the third standard deviation.

A curve with values below 165 mg.% in the first hour, 135 mg.% at one and one-half hours, and 125 mg.% at two hours was classified as a normal glucose tolerance test. Values between 165 and 196 mg.% at one hour, between 135 and 155 mg.% at one and one-half hours, and between 125 and 140 mg.% at two hours were regarded as indicative of borderline diabetes. A curve with values above 196 mg.% in the first hour, 155 mg.% at one and one-half hours, and 140 mg.% at two hours was designated as frank diabetes.

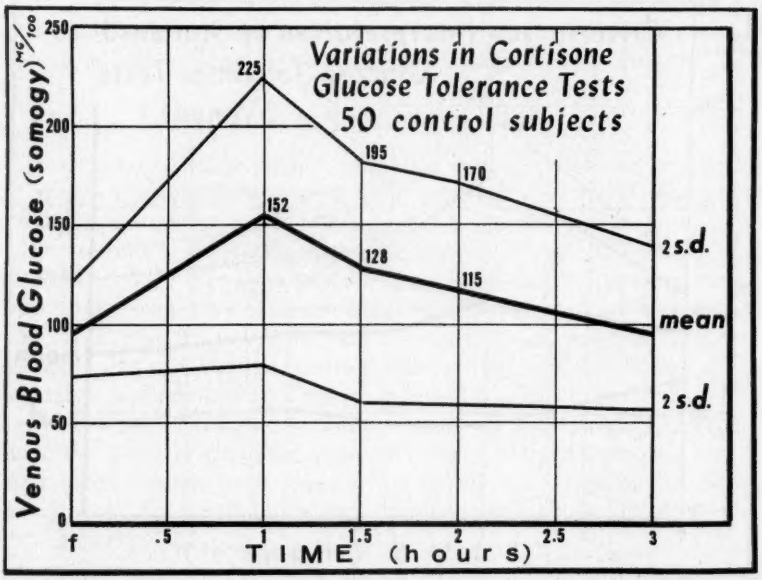

FIG. 2. Range of glucose tolerance following cortisone priming in 50 control subjects.

Of the 92 apparently normal subjects with no family history of diabetes who were included in this study, 85 (93%) were nondiabetic, four (4%) were borderline, and three (3%) were found to have frank diabetes. Of 83 subjects with diabetic relatives, 73 (89%) were nondiabetic, four (5%) were borderline, and five (6%) proved to have frank diabetes.

Cortisone-Glucose Tolerance Tests: In Figure 2 are shown our criteria for interpretation of the cortisone-glucose tolerance test in 50 control subjects with no family history of diabetes and with normal standard glucose tolerance tests. Although several of these subjects were found to have elevated curves after taking cortisone, the data from these individuals were

included in arriving at our criteria, since careful study revealed no valid reason for discarding them from the control group. The mean age was 45 years, and the venous glucose values taken while fasting, at one hour, one and one-half hours, two hours, and three hours were expressed as "true" blood sugar levels. A similar statistical analysis was applied to these results as to the results of the standard glucose tolerance tests.

A curve with values below 225 mg.% in the first hour, 195 mg.% at one and one-half hours, and 170 mg.% at two hours was considered to be a negative response, and a curve with values above these levels at the same time intervals was considered to be a positive response to cortisone.

Fifty-four (94%) of 58 nondiabetic individuals with no family history of diabetes had a negative response, and four (6%) a positive response. In the borderline group of only three subjects with no family history of diabetes, all three (100%) had a positive response. Among nondiabetic subjects with diabetic relatives, 34 (77%) had a negative response and 10 (23%) a positive response to the cortisone-glucose tolerance test, and of the three borderline individuals two (67%) had a positive and one (33%) a negative result.

TABLE 1

Comparison of Means and Standard Deviations for Blood Sugars During Standard Glucose Tolerance Tests in Subjects With and Without Family History of Diabetes

	No Family History	Family History
Fasting	88 ± 10.9	88 ± 10.4
1 hr.	105 ± 30.6	116 ± 31.6
1½ hrs.	88 ± 22	104 ± 27.4
2 hrs.	87 ± 18	95 ± 19.1
3 hrs.	80 ± 17.3	86 ± 14.4

Note: The difference between the means is not statistically significant.

Further statistical comparison between the subjects with and without a family history of diabetes is demonstrated in Table 1. Here are compared the means and the standard deviations for the control group with no hereditary predisposition and those for the relatives of diabetics. From these data it is evident that there is little difference in the mean blood sugar levels and that, based on the standard glucose tolerance test, a slightly lower than normal glucose tolerance is found in the relatives of diabetics.

Results of standard glucose tolerance testing and cortisone-glucose tolerance testing in those subjects with no family history of diabetes as compared to the individuals with a hereditary background are shown in Figure 3.

Seven of 61 cases with no family history of diabetes demonstrated a "positive" response to the cortisone-glucose tolerance test as compared to 12 of 47 cases in the group with a hereditary predisposition. A comparison of the average blood sugar level and the range of blood sugar at one hour, one and one-half hours, and two hours for those individuals with positive cortisone-glucose tolerance tests in the two different groups is demonstrated in Table 2. It can be seen that in this small group there was a similar

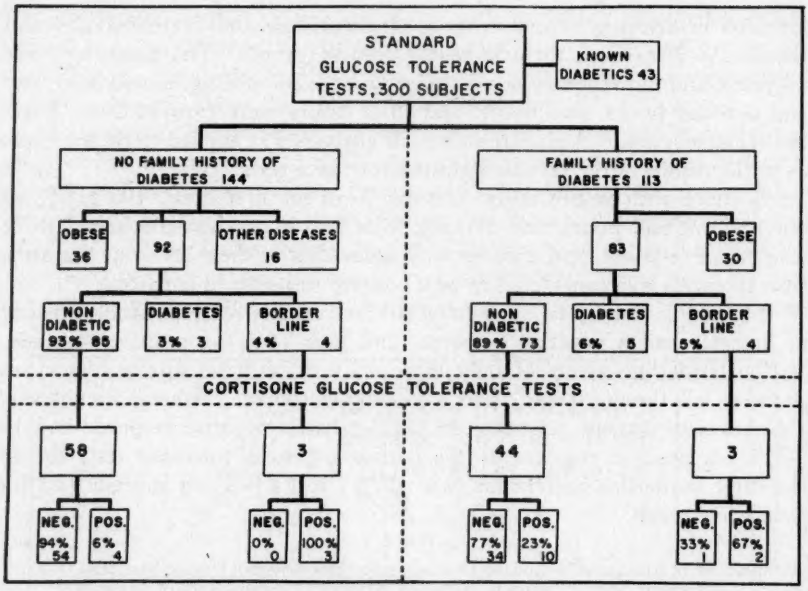

FIG. 3. Classification of subjects included in study and comparison of results of standard and cortisone-glucose tolerance tests according to hereditary background.

response to glucose alone and to the cortisone-glucose combination for the individuals with "positive" responses.

Comparison of Response to Glucose and Cortisone-Glucose: In order to evaluate the response to cortisone alone the differences between the mean two-hour glucose values after glucose alone and after cortisone-glucose in the group with no family history of diabetes is compared with similar values of the subjects having a hereditary background (Table 3).

TABLE 2

Comparison of Average Blood Sugar and Range of Blood Sugar for Subjects With "Positive" Response to Cortisone-Glucose Tolerance Test

		Average Blood Sugar	
		No Family History Diabetes (Mean Age 51)	Family History Diabetes (Mean Age 47)
1 hr.	Std. GTT*	141 (94–177)†	130 (95–178)
	After cortisone	239 (212–275)	235 (208–266)
1½ hrs.	Std. GTT	120 (60–148)	122 (96–170)
	After cortisone	219 (198–269)	212 (178–278)
2 hrs.	Std. GTT	107 (70–133)	101 (82–140)
	After cortisone	188 (162–268)	191 (144–246)

* Standard glucose tolerance test.
† Range of value is given in parentheses.

TABLE 3

Comparison of the Mean Two-Hour Blood Sugar During Both Standard and Cortisone-Glucose Tolerance Tests for Subjects With and Without Genetic Predisposition for Diabetes Mellitus

	No Family History Diabetes	Family History Diabetes
Age (mean)	45	42
Std. GTT*	Control subjects	Control subjects
2 hr. blood sugar (mean)	87 mg. %	95 mg. %
C-GTT†	Control subjects	Control subjects
2 hr. blood sugar (mean)	115 mg. %	133 mg. %
Difference Between C-GTT and std. GTT at 2 hrs.§	2 hr. B.S. after C-G‡ (mean) 28 mg. %	2 hr. B.S. after C-G (mean) 38 mg. %

* Standard glucose tolerance test (70 subjects).
† Cortisone-glucose tolerance test (50 subjects).
‡ Cortisone-glucose.
§ Not significant between the two groups of subjects.

The mean two-hour blood glucose value for the control subjects with a family history of diabetes was 95 mg.% after glucose alone and 133 mg.% after cortisone-glucose. The mean elevation of 38 mg.% after cortisone-glucose was, of course, greater than that (28 mg.%) of the group with no family history of diabetes, but lacked significance.

DISCUSSION

It is difficult to fix criteria for interpretation of normal glucose tolerance because of the various levels reported for nondiabetic individuals, and because there is some difference of opinion among clinicians as to what does and does not constitute diabetes mellitus. However, in the absence of cardinal signs and symptoms the diagnosis usually is made by demonstrating a decreased tolerance to glucose.

In this study we chose first to establish our own criteria for interpretation of standard and cortisone-glucose tolerance tests from a statistical analysis of our data, realizing, however, that there are limitations to the statistical method and that from statistics may emerge a picture which is seldom, if ever, encountered by the physician in handling an individual with diabetes mellitus. It is of interest that our values, derived statistically, compare favorably with other large series of standard glucose tolerance tests,[7, 8] and that our values for the line of demarcation between nondiabetics and diabetics are similar to those values established arbitrarily as criteria in other reported investigations.

The diabetic relatives in this study were not limited to offspring, siblings, or parents of known diabetics, and perhaps this fact accounts for the higher percentage of nondiabetic relatives found on the basis of the standard glucose tolerance test alone.

Stress is recognized as an important precipitating factor in diabetes,

and the stress of pregnancy [9] has long been known to be associated with the onset and precipitation of this metabolic disorder. There now exists the concept of a "prediabetic state," and the influence of steroids in producing a temporary diabetic state has been responsible for evolution of the cortisone-glucose tolerance test that can be utilized in the study and diagnosis of disorders of carbohydrate metabolism and in attempts to predict the eventual development of diabetes in an individual.

Our criteria for interpretation of the cortisone-glucose tolerance test in normal individuals (mean age 45 years) with no family history of diabetes and a normal standard test may seem to be elevated when compared to other reported criteria for cortisone-glucose tolerance in groups with an average age of 20 and 30 years. We find that our criteria are very similar to those of German,[10] reported in his statistical report on non-obese men 30 years of age, if reductions are made in his Folin-Wu values in comparison with our "true" blood sugar levels. It has been demonstrated by West that older subjects are more likely to exhibit positive responses to steroid priming.

It is agreed that individuals with a genetic predisposition may be more likely to respond with elevated levels of blood glucose after both cortisone and glucose administration; however, there is some question whether these people may be unusually responsive to cortisone itself. Our results, similar to observations of West with subjects whose parents were both diabetic, would imply that perhaps the cortisone-glucose tolerance test is not always specific in detecting susceptibility to diabetes in subjects with a hereditary background for the disorder.

Summary

Three hundred active subjects including controls, diabetics, and relatives of diabetics were subjected to a standard glucose tolerance test and in 150 of these individuals the test was repeated after cortisone was administered orally. Simultaneous capillary and venous glucose levels were determined during all tests.

Criteria for interpretation of both standard and cortisone-glucose tolerance tests are presented, based upon a statistical analysis of data obtained from normal patients who had no diabetic relatives.

Ninety-three per cent of apparently normal subjects with no family history of diabetes were found to be nondiabetic, 4% were borderline, and 3% were found to have frank diabetes after a standard glucose tolerance test. After a similar test for the diabetic relatives, 90% were nondiabetic, 5% were borderline, and 5% proved to have frank diabetes.

Ninety-four per cent of nondiabetic individuals with no genetic predisposition had a negative response and 6% a positive response to the cortisone-glucose tolerance test, whereas 76% of the nondiabetic subjects with diabetic relatives had a negative and 24% a positive response.

The response to cortisone itself in the subjects with a family history of diabetes was greater than the cortisone response of the group with no

hereditary background; however, this increase in response lacked significance ($p > 0.9$). These data indicate that there is limitation to the ability of the cortisone-glucose tolerance test in the prediction of diabetes mellitus.

Summario In Interlingua

Le detection del diabetico potential es un objectivo principal de multe clinicos e investigatores. Es presentate le principios del evalutation e del investigation de tolerantia pro glucosa e pro cortisona-glucosa in alteremente normal subjectos e in subjectos con antecedentes hereditari de diabete. Tres centos subjectos active—incluse un gruppo de controlo, diabeticos, e consanguineos de diabeticos—recipeva un special preparation dietari ante le test standard de tolerantia pro glucosa e le test del tolerantia pro cortisona-glucosa. Determinationes simultanee del nivellos de glucosa in sanguine capillari e venose esseva facite in specimens prendite in stato jejun e a intervallos de trenta minutas durante tres horas per medio de un modification del technica de Somogyi-Nelson. Criterios pro le interpretation de iste tests es presentate super le base de un analyse statistic del datos obtenite in patientes normal sin consanguineos diabetic. In le gruppo de apparentemente normal subjectos sin antecedentes familial de diabete, 3% del subjectos esseva diabetic e 4% esseva in limbo. Esseva trovate in le gruppo de consanguineos de diabeticos que 6% del subjectos esseva patentemente diabetic e 5% esseva lo presumitemente. Sex pro cento del subjectos nondiabetic sin predisposition genetic habeva un responsa positive al test de tolerantia pro cortisona-glucosa, durante que 23% del subjectos nondiabetic con consanguineos diabetic habeva un responsa positive. Le responsa a cortisona per se esseva plus marcate in le subjectos con antecedentes familial de diabete que in le subjectos sin tales. Tamen, le augmento del responsa esseva sin signification statistic (P plus que 0,9). Iste datos indica que il existe un limitation del capacitate del test de tolerantia pro cortisona-glucosa a predicer diabete mellite.

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VIRILIZING CONGENITAL ADRENAL HYPERPLASIA: TWENTY-FIVE YEARS LATER *

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ONE of the most remarkable advances in clinical endocrinology has been the elucidation of the pathogenesis, clinical features, and treatment of congenital adrenal hyperplasia.[1-3] In the fetal adrenal cortex of affected persons, synthesis of hydrocortisone is defective owing to a deficiency of specific hydroxylating enzymes. A larger amount of adrenocorticotrophin (ACTH) stimulation of the adrenal is necessary to produce that blood level of hydrocortisone which will in turn suppress and regulate pituitary production of ACTH. Thus, an equilibrium is established at a supranormal level of ACTH release, which causes morphologic hyperplasia of the adrenal cortex. The functional concomitant is increased steroidogenesis, with accumulation of androgenic by-products, which is reflected in increased urinary excretion of 17-ketosteroids and pregnanetriol. The administration of cortisone in physiologic replacement doses restores normal pituitary-adrenal balance. This also provides a diagnostic confirmation by reducing the elevated 17-ketosteroid and pregnanetriol excretion, and serves as a rational mode of therapy, since ACTH and adrenal androgen production are suppressed.

Excessive androgen production begins in fetal life before the external genitalia are formed. Thus, in the female infant, enlargement of the clitoris and varying degrees of labial fusion are observed at birth. In the male infant, the genitalia are usually normal at birth, but precocious enlargement of the penis occurs within the first few years of life. Rapid growth, muscular development, premature appearance of epiphysial centers (accelerated bone age), and early appearance of sexual hair are common to both sexes. Linear growth, while accelerated, is often terminated before full height is attained because epiphysial closure is also premature. The female undergoes progressive virilization, and breast development and menstruation may be either scant or absent. In the untreated adult female, pregnancy will not occur. The affected male child has been described as a "little Hercules," but the testes usually remain small because of suppression of pituitary gonadotrophins by adrenal androgens. Little is known about the reproductive potential of the affected male adult.

About one-fourth of the cases will exhibit the syndrome of infantile adrenal insufficiency with salt-wasting. The etiology of this syndrome is poorly understood, but there is probably defective aldosterone production.

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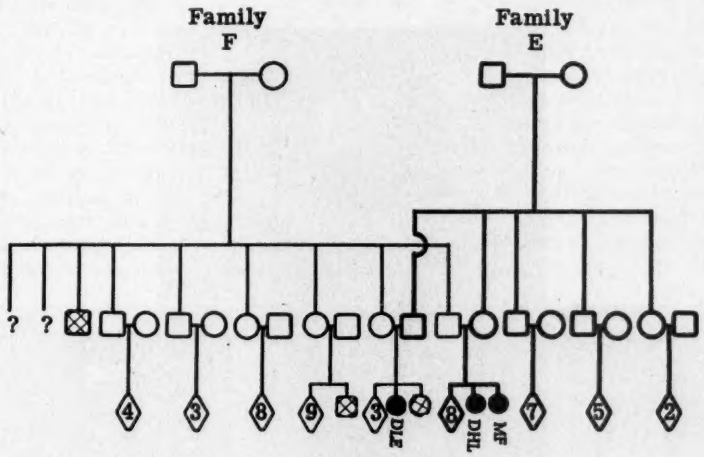
After a few years of continuous cortisone therapy, this salt-wasting tendency appears to diminish markedly.[4] A rare type of congenital adrenal hyperplasia complicated by hypertension is caused by a specific defect in 11-beta-hydroxylation of hydrocortisone, with overproduction of the mineralocorticoid, desoxycorticosterone.[5]

Treatment with cortisone or with related corticosteroids will correct or prevent the accelerated growth and virilizing features of this disorder if it is begun in infancy or in early childhood. Desoxycorticosterone and salt will also be necessary if salt-wasting is present. Amputation of the clitoris and plastic reconstruction of the external genitalia are often necessary in the female child. Cortisone therapy, if begun after accelerated growth



CONGENITAL ADRENAL HYPERPLASIA

FIG. 1. Pedigree showing "double cousin" relationship of the two biologic families. Affected subjects are represented by black, possibly affected subjects by cross-hatching. The numerals represent the number of unaffected persons in each sibship.

is well established, will still cause feminization and permit pregnancy to occur in the adult.

In 1935 O'Farrell reported clinical and surgical observations on three female patients whose condition he designated "hereditary hermaphroditism."[6] Subsequently, all three patients were recognized as cases of congenital adrenal hyperplasia. Observations made on two of these patients a quarter-century later form the principal basis of this report.

Two of the three patients were sisters. The third was a "double cousin" of the first two, a relationship produced when two members of one sibship mate with siblings of another sibship, as shown in Figure 1. Three other persons in this pedigree had genital anomalies similar to those of our

patients. A member of the preceding generation lived as a male, and died at age 20. Another was considered a male by his parents and died at age two. The third, a sibling of case 1, was considered to be a female by the parents and also died at age two. No autopsies were done. The possible role of adrenal insufficiency in the early demise of these children cannot be assessed. The succeeding generation, not shown in the figure, is large but no other affected persons are known.

Case Reports

Case 1. The first patient, D.L.E. (O'Farrell's case 2) was born in 1924, and genital abnormality was noted at birth. At four months she was examined by the late Dr. James E. Thompson, Professor of Surgery at the University of Texas Medi-

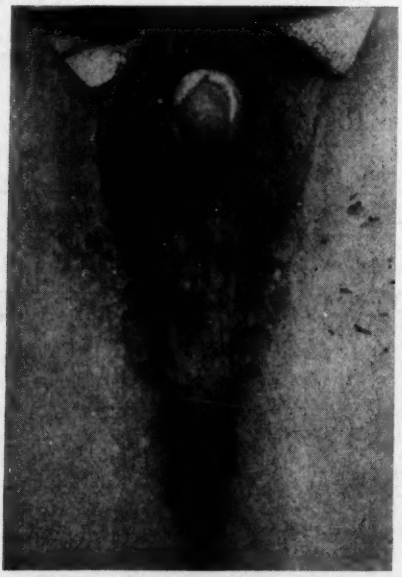


Fig. 2. Case 1, age 9. Note enlarged clitoris, escutcheon, and absent vaginal outlet. (Reprinted by permission from J.A.M.A. 104: 1968, 1935.)

cal Branch, who described an enlarged clitoris without vaginal orifice, but a uterus was identified on rectal examination. During infancy there were no symptoms to suggest a salt-losing tendency. When seen by Dr. O'Farrell at the age of nine, she appeared to be "at least two years older." The clitoris was large. No vaginal orifice was present. Pubic hair was profuse, and of male distribution (Figure 2). At surgery, uterus, tubes, and imperforate vagina were identified. The clitoris was amputated and plastic revision of the vagina accomplished. Menses began at age 11, but were irregular and so scant that she never had to wear pads. By age 18, heavy growth of beard, chest hair, and body hair had occurred, with slight breast development. She completed high school and had held several jobs. However, she was reluctant to go far from home. She mingled socially with men and women,

but always felt "different." She experienced attraction to the opposite sex, but had grave doubts about her ability to function as a normal woman in a marital relationship. She presented herself at our clinic in 1954 at age 29 requesting examination to see if anything could be done to make her appearance more feminine and to reduce body hair.

The principal physical findings were apparent on inspection (Figure 3*a*). Vital signs were normal. The blood pressure was 120/80 mm. Hg. She was 5 feet 2 inches tall, approximately the same height as other females in her family. Her build was masculine with broad shoulders, narrow hips, and muscular arms and legs. A coarse beard was present over the face and neck, which she shaved, and the arms, legs, chest, perineum, buttocks, and lower abdomen were quite hirsute. Scalp hair was thin and temporal recession was noted. Breasts were quite small. On pelvic examination a small clitoral stump could be felt. A 4 cm. left ovarian cyst was felt, which has subsequently waxed and waned in size. Laboratory study was not unusal except for the excretions of 30, 44, and 42 mg. of 17-ketosteroids/24 hr. (normal, 5 to 15 mg./24 hr.), which rose to 75 and 105 mg. after ACTH (25 mg. over an eight-hour period intravenously). A later special study [7] provided evidence that this patient could excrete large quantities of pregnanetriol in the urine (Figure 4).

The clinical and laboratory data supported a diagnosis of congenital adrenal hyperplasia. The fall in 17-ketosteroid excretion after cortisone administration is shown to be prompt and pronounced, and to be maintained through treatment with a variety of glucocorticoid agents, which included cortisone and hydrocortisone by mouth, cortisone acetate and repository hydrocortisone acetate intramuscularly, and oral prednisone and triamcinolone (Figure 5). The initial goal of therapy was to maintain normal 17-ketosteroid levels, and this occurred with all medications. On oral administration of 80 mg. daily of hydrocortisone and later on 12 mg. daily of

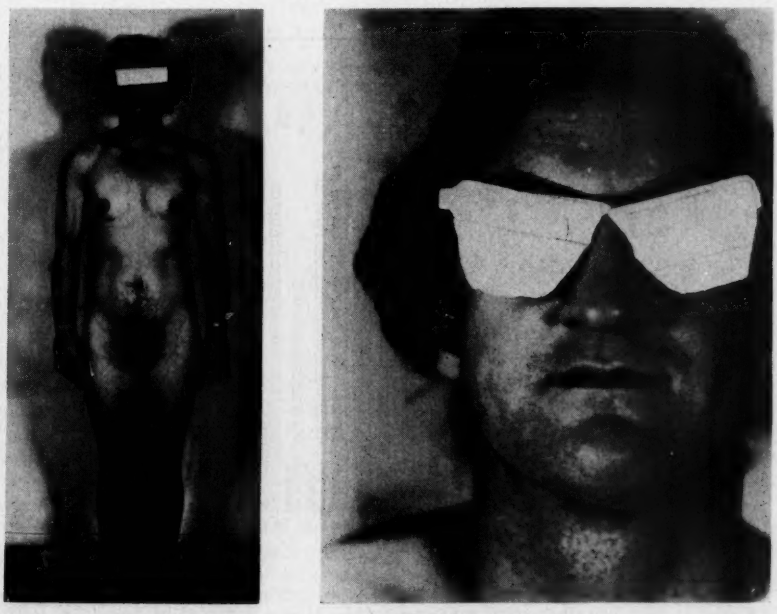


FIG. 3*a*. Case 1, age 29, before treatment.

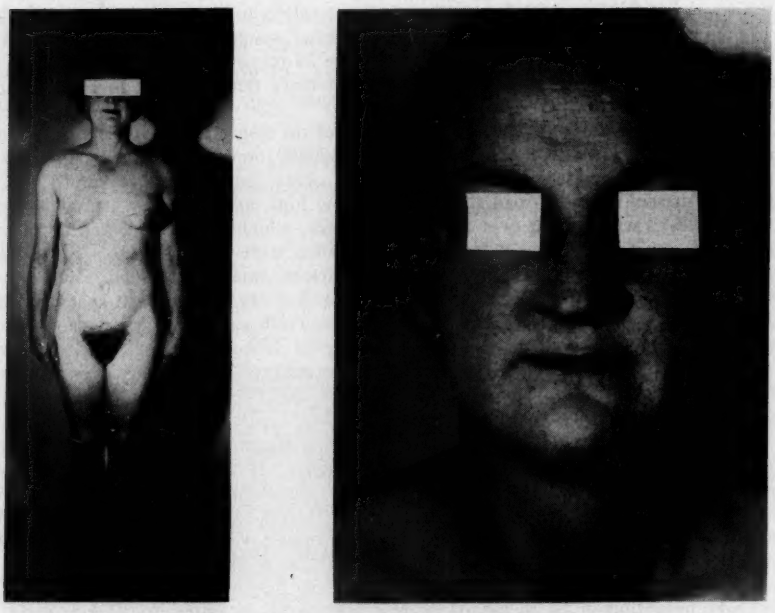


FIG. 3*b*. Case 1, age 35, after six years of corticosteroid therapy.

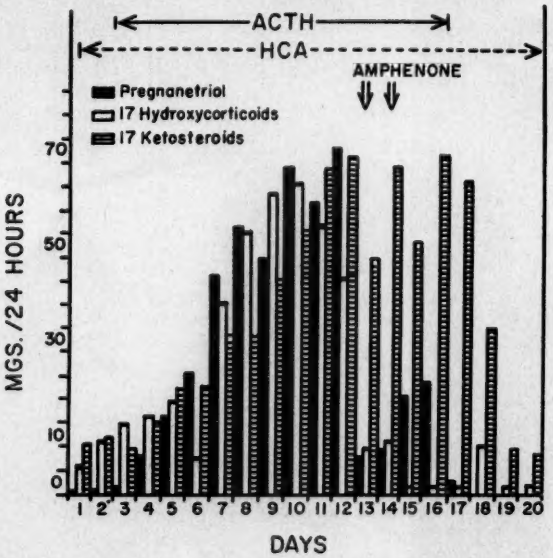


FIG. 4. Case 1. Excretion of 17-ketosteroids, 17-hydroxycorticoids, and pregnanetriol during ACTH administration, while endogenous ACTH is suppressed by repository hydrocortisone acetate. (Reprinted by permission, Tex. Rep. Biol. Med. 15: 381, 1957.)

triamcinolone, the patient developed early signs of hypercortisonism (increase in weight, rounded facial contour, and mild hypertension) associated with relatively low 17-ketosteroid values. Much lower doses of cortisone were required when given intramuscularly, as low as 50 mg. every fourth day. Two hundred milligrams of hydrocortisone acetate intramuscularly every second week was also satisfactory. Both triamcinolone and prednisone have been orally effective, although the therapeutic margin with triamcinolone may be relatively narrow. In this patient prednisone has proved to be the most satisfactory oral agent for control of 17-ketosteroid excretion without side effects.

During the first few weeks of therapy there was a subjective sense of improvement and well being. Six months elapsed before we could be satisfied that reduction

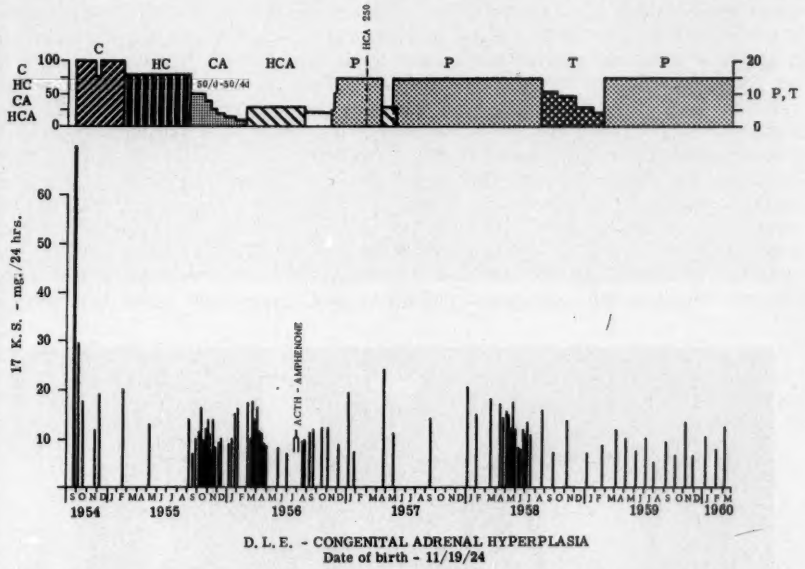


FIG. 5. Case 1. 17-ketosteroid excretion during corticosteroid suppressive therapy. C—oral cortisone; CA—IM, cortisone acetate; HC—oral hydrocortisone; HCA—repository IM hydrocortisone acetate; P—oral prednisone; T—oral triamcinolone. The period indicated by "ACTH-Amphenone" is shown in FIG. 4.

in body and facial hair and increase in scalp hair had occurred. Breasts were fuller at this point, and two years later had become pendulous. Menses remained scant but have been regular. She still has a few coarse facial hairs, but shaves rarely. Prior to therapy, we did not determine whether menses were ovulatory, but since treatment definite evidence of ovulation has been obtained from basal body temperature curves and endometrial biopsies. The change in appearance from a recent photograph is quite apparent, and she weighs only five pounds more (Figure 3*b*).

After three years of therapy, a psychologic consultant (Dr. Austin Foster) reported a "continuing tendency to feel lost and socially isolated . . . very much dependent on her parents for support and guidance . . . anxious, tense, and unsure of herself most of the time. She tries to compensate for feelings of inadequacy by exaggerated displays of competence, sophistication, and independence. These fal-

lacious displays are punctuated by pleas for reassurance and support. Her sexual adjustment is the source of much anxiety. She tries to intellectualize and pattern herself in the role of a woman, but her insecurity makes her efforts a strained performance."

Case 2. The second patient, D.H.L. (O'Farrell's case 1), is one of two sisters, both double cousins of D.L.E. She was born in 1914 and her genital defect was recognized at birth. By the age of nine years she had reached her full adult height and had axillary and pubic hair. When seen by Dr. O'Farrell at age 19, she was described as very masculine but "of poor muscular development." He found a "well developed penis," appearing hypospadic, rudimentary labia, and a "horizontally split vagina" with normal-size opening and of three-inch depth. Heavy facial hair growth was present and breasts were flat. Uterus and ovaries were identified at operation, the enlarged clitoris was amputated, and plastic repair was performed on the vagina. She married more than 20 years ago and has had normal intercourse, but never became pregnant although no contraceptives were used. She had no significant change in her condition until age 35, when she sought medical attention elsewhere for an eye infection and her amenorrhea and previous genital defect were noted. She was apparently advised to take stilbestrol, 5 mg. daily on a cyclic basis, which she continued for several years. She later reduced the dose to 1 mg. on her own initiative, and finally stopped the drug because of lower abdominal swelling so pronounced that she appeared to be pregnant. While on this regimen, menses began, breast development occurred, and there was marked reduction of facial hair. These beneficial effects persisted despite discontinuance of stilbestrol. She was referred to our clinic in 1958 at age 42 by her cousin because of left lower quadrant premenstrual pain of several months' duration. Since this pain disappeared rather promptly, it

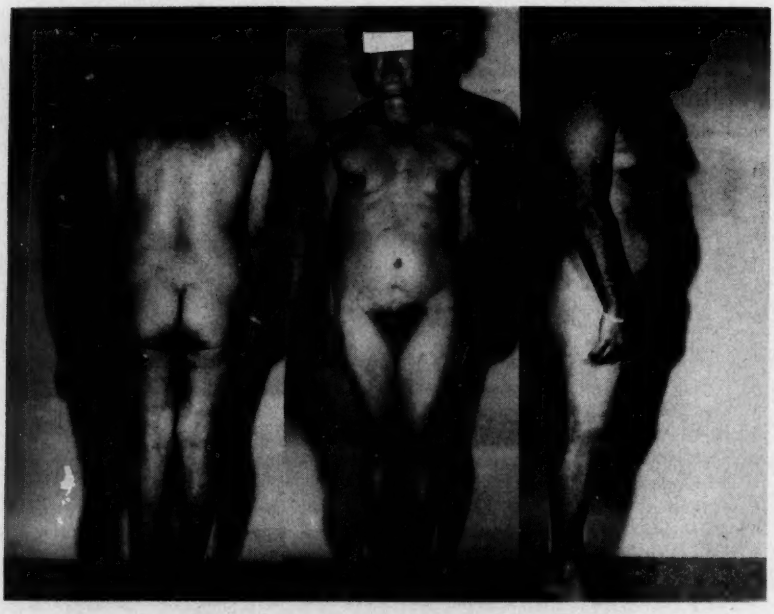


FIG. 6*a*. Case 2, age 42, before treatment.

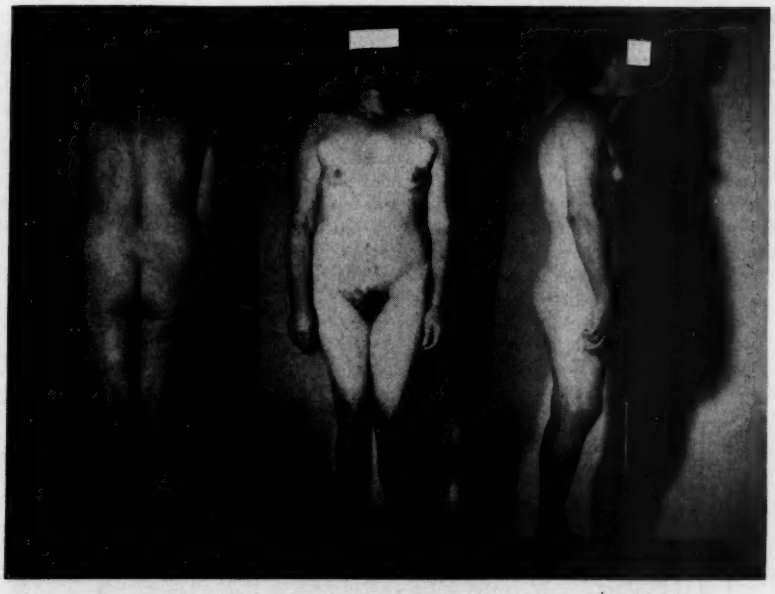


FIG. 6*b*. Case 2, age 44, after two years of corticosteroid therapy.

seems probable that this merely represented an acceptable way for her to present herself for evaluation of her adrenal abnormality. Her physical signs were chiefly those visible on inspection (Figure 6*a*). Her vital signs were normal. Blood pressure was 134/80 mm. Hg. She was lean and muscular, and presented a weathered,

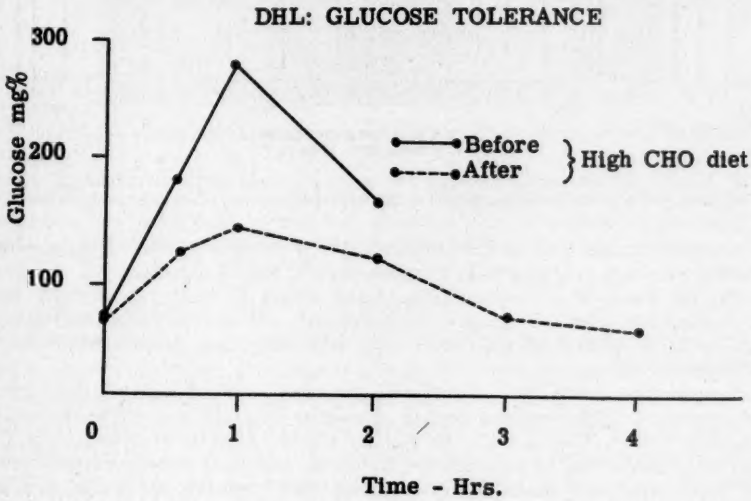


FIG. 7. Case 2. Glucose tolerance test before and after "carbohydrate loading."

square-jawed appearance. Head hair was normal. Facial hair consisted of scattered coarse hairs that rarely required removel. She stood 60 inches in height, two inches less than that recorded by Dr. O'Farrell in 1934. This apparent loss in height is probably referable to a rather pronounced dorsal kyphosis. The breasts were small though distinctly larger than those of patient D.L.E. prior to treatment. There were a masculine escutcheon and hirsute extremities and perineum. There was considerable postoperative scarring at the introitus, and the labia minora were fused anteriorly. No abnormalities were detected on bimanual examination. Usual laboratory studies were within normal limits except for an abnormal glucose tolerance test. The patient confessed that she lived on beefsteak, lettuce, and tomatoes. A repeat glucose tolerance test after carbohydrate feeding was normal (Figure 7). Excretions of 17-ketosteroids were 28, 21, and 41 mg./24 hr. During two days of ACTH stimulation

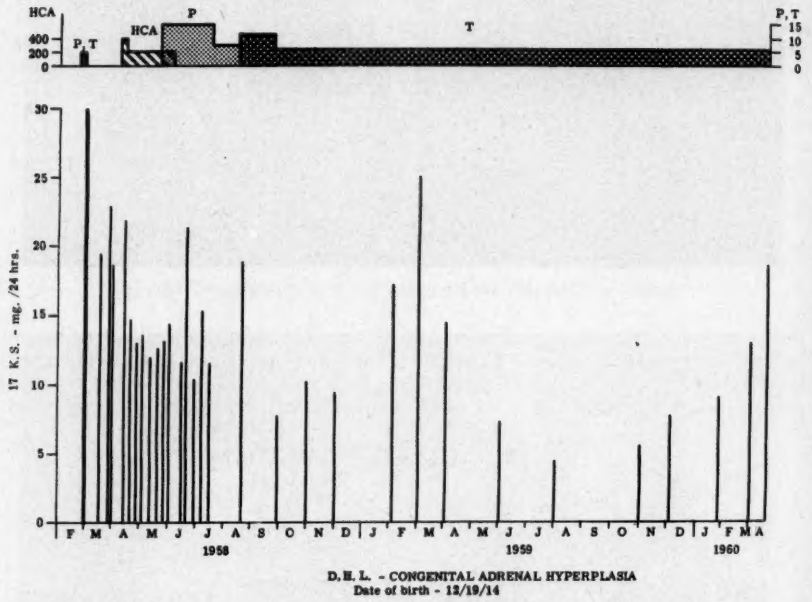


FIG. 8. Case 2. 17-ketosteroid excretion during corticosteroid suppressive therapy. HCA—repository IM hydrocortisone acetate; P—oral prednisone; T—oral triamcinolone.

(25 mg. over an eight-hour period intravenously) 17-ketosteroid excretion was 43 mg. each day. Urinary pregnanetriol excretions were 32 and 24 mg./day.

On the bases of a characteristic genital defect at birth, an affected sister and cousin, and elevated urinary 17-ketosteroid and pregnanetriol excretion, a diagnosis of congenital adrenal hyperplasia was made, and corticosteroid therapy was begun.

Suppression of urinary 17-ketosteroid excretion occurred with all three agents used: repository hydrocortisone acetate at weekly intervals, and triamcinolone and prednisone orally (Figure 8). She had no untoward initial symptoms, but after being on triamcinolone, 12 mg. daily for six weeks, developed a distinct appearance of mild hypercortisonism which slowly regressed after reduction of dosage to 6 mg. daily. There has been a definite reduction in body hair, and pubic hair has now a

feminine appearance (Figure 6*b*); facial hirsutism was already so slight as not to provide a good criterion of therapy. Otherwise her appearance and status are little changed.

Case 3. The third patient, M.F. (O'Farrell's case 3), sister of D.H.L., was never seen in our clinic. She gave a similar history of genital abnormality at birth, precocious growth and sexual development, and amenorrhea. When seen by Dr. O'Farrell at age 24, she had a masculine habitus, a heavy beard, increased body hair, and no breast development. The clitoris was enlarged (Figure 9). Uterus and ovaries were identified at laparotomy, and the clitoris was amputated. She had a few scanty menstrual periods subsequently, probably related to hormone injections. At age 28 she sought treatment at the Johns Hopkins Hospital. A diagnosis of congenital adrenal hyperplasia was made and exploration of both adrenals with

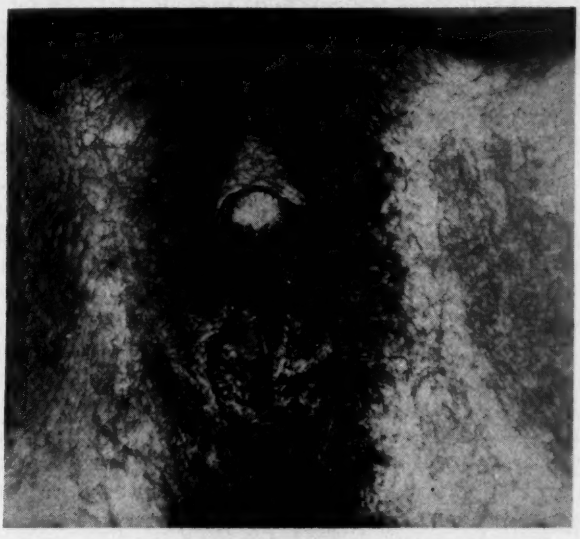


FIG. 9. Case 3, age 24. External genitalia. (Reprinted by permission from J.A.M.A. **104**: 1968, 1935.)

removal of an enlarged left adrenal performed. Some years later she was accidentally drowned. Her sister believes that her hirsutism may have become somewhat less marked, but that she was basically little changed by her surgical procedure.

DISCUSSION

The presence of a genital defect at birth, indicating adrenal hyperplasia and excessive androgen production prenatally, clearly places these patients in the category of congenital adrenal hyperplasia. Although medical attention had been obtained, and in one case a correct diagnosis had been made, the unavailability of satisfactory therapy provided us the unique opportunity to observe the effects of this syndrome in the untreated state after 29 and 42 years, respectively. Early diagnosis and suppressive therapy should eventu-

ally eliminate this type of patient altogether. However, if it be assumed that the majority of those affected persons who did not have adrenal insufficiency were capable of surviving into adulthood, there should have been a considerable backlog of patients who survived to maturity prior to 1952, when cortisone suppressive therapy was introduced by Wilkins. The two patients reported here are the only instances in which the congenital form of virilizing adrenal hyperplasia has been diagnosed in a large teaching hospital. This would suggest that many of these patients did not survive in the untreated state, or that they have been reluctant to present themselves to physicians for treatment.

The latter is suggested by the behavior of our case 2, who endured three years of urging by her cousin before coming to clinic, and even then employed an apparent subterfuge to seek advice. This is perhaps not surprising, since she had made an apparently satisfactory heterosexual adjustment for over 20 years, and had long since accepted her condition as being irremediable, but tolerable. She did not expect even her husband to accept her on these terms, however. She never disclosed to him her previous medical history, and made all her clinic visits when he was out of town.

The patient described as case 3 is said by her sister to have had a normal heterosexual adjustment, and was engaged to be married when she was drowned. The social adaptation of all three of these patients stands in marked contrast to the sociopathic behavior of several of the patients described long before the cortisone era in Young's classic monograph.[8]

The primary goal of therapy in cases 1 and 2 was to reduce hirsutism and to produce a more feminine body configuration. Therapy was strikingly successful in case 1. Hirsutism was markedly reduced, breast development occurred, and body contours became more feminine. It is noteworthy that at least two years was required for maximal therapeutic benefit. In case 2, the most striking effect has been a further reduction in hirsutism. The history of persistent feminization after estrogen withdrawal in this patient is intriguing, if accurate. The continued elevation of urinary 17-ketosteroids and pregnanetriol suggest that no fundamental change in the adrenal cortex had occurred.

Both these patients had come to understand that they were "different" from other women. A remarkable incidental benefit of therapy has been the achievement of a sense of being "normal," which appears to go beyond the simple objective change in appearance. That this remains imperfect, however, is reflected in the psychologic evaluation of case 1, three years after therapy was begun.

It has been necessary to consider whether therapy should be continued indefinitely. Although there are relatively few patients of this age under therapy at present, the internist will be inheriting a larger number of such patients as they outgrow the pediatric age range. There is no evidence to date that the adrenocortical secretory pattern in congenital adrenal hyper-

plasia undergoes change toward normal with aging. Even those subjects with disordered electrolyte regulation who "outgrow" the need for mineralocorticoid replacement after several years of cortisone therapy have been shown to have a diminished ability to conserve salt. Thus, it can be assumed that in the female therapy must be continued throughout the reproductive period in order to maintain normal femininization and fertility.

At present, it is planned to continue therapy in these two patients beyond the reproductive period for the following reasons: (1) Abnormal hirsutism would probably recur if therapy were discontinued even after the menopause; (2) A regulated supply of glucocorticoid and androgen is preferable to the disordered secretory pattern which would recur if therapy were discontinued; (3) Finally, there is some evidence that prolonged adrenal hyperplasia may lead to the development of adrenal carcinoma.[9] If it be assumed that adequate suppressive therapy permits regression of the morphologic hyperplasia, the development of carcinoma may be prevented. This line of thinking would argue not only for the treatment of adrenal hyperplasia at whatever age the patient presented, but also for continuing therapy indefinitely in male patients.

While the ultimate criterion of successful therapy is the regression of the virilizing changes, immediate control of dosage is best gauged by the urinary excretion of 17-ketosteroids or pregnanetriol. With proper dosage and route of administration, cortisone, hydrocortisone, or any of the synthetic glucocorticoids will suppress 17-ketosteroid excretion satisfactorily without undue side effects. Cortisone and hydrocortisone are more effective by injection, because of the slower rate of disappearance from the blood after parenteral administration. Consistent pituitary suppression is related more to average blood level of corticosteroid, while side effects are related to total dosage. Both prednisone and triamcinolone have proved to be satisfactory for oral maintenance of these patients. It is important to remember that during therapy, the patient is entirely dependent on his exogenous supply of corticosteroid. During periods of stress, he may require higher dosage, and he must understand that therapy should never be discontinued except under medical supervision.

While no conclusions can be drawn from the pedigree of these patients, the familial incidence is compatible with the conclusions of Childs, Grumbach, and Van Wyk[10] that congenital adrenal hyperplasia is a genetically determined disorder with a recessive mode of inheritance. The similarity of the manifestations in all three patients is also in accord with their observations that all cases occuring within a family tend to have similar manifestations. This would suggest that salt-losing adrenal insufficiency was not a factor in the early demise of the "possibly affected" children shown in the pedigree. Measurements of 17-ketosteroid excretion were made on the urine of about 20 immediate relatives of these patients, but no abnormality was found. Childs et al. suggested that heterozygotes may have an abnormally high

excretion of pregnanetriol after administration of ACTH, but this was not studied in the relatives of our patients.

Summary

Follow-up observations are described on three adult female patients with virilizing congenital adrenal hyperplasia, who were first described in 1935. These patients are members of the same pedigree, which includes three other possibly affected persons. Two of the patients survived into the cortisone era, and have been treated with corticosteroid suppressive therapy. In one, in whom therapy was begun at age 29, marked femininization occurred after two years. In the other, in whom therapy was begun at age 42, distinct reduction in hirsutism occurred. It is proposed that corticosteroid therapy of the patients reported should be continued indefinitely.

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Photocopies of Johns Hopkins Hospital records were supplied through the courtesy of Dr. Harry Chant.

Pregnanetriol determinations were obtained through the courtesy of Dr. George Clayton, Baylor Medical College.

Summario In Interlingua

Iste reporto describe observationes in duo patientes feminin con congenite hyperplasia adrenal qui recipeva nulle therapia corticosteroide ante que illas habeva attingite un etate adulte. Un reporto de plastic reparo genital effectuate in iste duo e un tertie simile caso appareva in 1935. Le tertie patiente esseva unilateralmente adrenalectomisate in un altere hospital e moriva plus tarde, ante le advento del era de cortisona. Duo del tres patientes esseva sorores. Le tertie esseva un cosina de illas per ambe parentes. Tres altere possibilemente afficite personas esseva trovate in le arbore genealogic de iste tres feminas. Ambe le patientes hic reportate habeva defectos genital al nascentia e subsequentemente progressive virilisation—sin antecedentes de insufficientia adrenal—e elevate valores del excretion urinari de 17-cetosteroides e pregnanetriol. In le prime patiente, un therapia suppressive a corticosteroide esseva initiate al etate de 29 annos, con le consequentia de un pronunciate femininisation e reduction del hirsutismo. Le therapia initiate in le secunde patiente al etate de 42 annos esseva sequite de un distincte reduction del hirsutismo, ben que le femininisation esseva minus marcate. Alterationes benefic in capillatura e configuration corporee occurreva gradualissimemente. Le uso oral de corticosteroides synthetic in le appropriate dosage, specialmente prednisona, es associate con un suppression de 17-cetosteroides urinari e un satisfacente responsa clinic sin adverse effectos lateral. Es presentate argumentos in favor del continuation "pervital" del therapia in patientes con congenite hyperplasia adrenal.

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RHEUMATOID PATIENTS AFTER FIVE OR MORE YEARS OF CORTICOSTEROID TREATMENT: A COMPARATIVE ANALYSIS OF 183 CASES * †

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THIS report summarizes the status of 183 patients with rheumatoid arthritis after a period of continuous corticosteroid treatment for five years or longer.

The treatment program always included increased rest, appropriate physical measures, therapeutic exercises, adequate diet, and analgesics. Of these 183 patients there were 47 for whom corticosteroid was the only additional treatment; in the remaining 136 patients corticosteroids were used after gold salts had been discontinued because they were either ineffectual or were not tolerated, so the gold therapy did not influence the course of illness.

Of these 183 patients 77% were females. At the end of observation when their status was determined the average age of these patients was 51 years.

The determination of status was based upon the separate considerations of functional capacity and joint structure according to the American Rheumatism Association criteria. Differences in classification at the beginning and end of the study were formulated from physical examinations and tests of functional capacity, roentgenograms of affected joints, and determinations of erythrocyte sedimentation rate. These patients have been observed for an average of 10 years. Corticosteroids used included those with proved antirheumatic effect as they were developed, beginning with cortisone acetate and ending with dexamethasone. These preparations were changed in most patients when new gluco-corticoids became available with the hope of lessened undesirable effects. The objective was to employ the least amount of steroid that would produce the desired effect, which always was only partial suppression of inflammation.

The daily dose of corticosteroid used for partial suppression of synovitis for the longest periods varied in accordance with the several drugs used. For example, the majority of patients (67%) receiving cortisone acetate required daily doses in excess of 50 mg. Patients treated with hydro-

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cortisone usually required from 25 to 50 mg. daily (69%). Forty-seven per cent of the patients treated with prednisone received from 10 to 14 mg. daily. Of the patients treated with methylprednisolone 41% received from 10 to 14 mg., 39% received 5 to 9 mg., and 20% received from 1 to 4 mg. daily. Of the patients treated with triamcinolone the majority (63%) received from 5 to 9 mg. daily. It may be seen on the accompanying Table 1 that the dosages of these several corticosteroids declined as their antirheumatic activity increased. These drugs were employed as they were introduced to clinical use and many of the patients were treated with a succession of these drugs in hopes of reducing the frequency of undesirable effects. It should be mentioned that these hopes were not always justified because only a few patients intolerant to one or another of the corticosteroids were able to use others.

After attempts to decrease the amount of steroid, during the last 15 months the average dose continuing in use became 45 mg. hydrocortisone,

TABLE 1

Daily Dose of Corticosteroids Used for Partial Suppression of Synovitis

Corticosteroid	Daily Dose in Mg.						
	1–4	5–9	10–14	15–19	20–24	25–30	50–100
	% of Patients Treated						
Cortisone				3		30	67
Hydrocortisone			3	1	19	69	8
Prednisone	8	31	47	10	4		
Methylprednisolone	20	39	41				
Triamcinolone	10	63	17	8	2		
Dexamethasone	100						

9 mg. prednisone, 6 mg. triamcinolone, 6 mg. methylprednisolone and 1 mg. dexamethasone. Slightly more than half of these patients are using prednisone or triamcinolone; one-fifth are using methylprednisolone.

RESULTS

The results are presented in two parts; the first part concerns functional changes, and the second deals with structural changes of the joints and adjacent tissues during treatment with corticosteroid drugs.

Changes in Function: Attempts have been made to describe objectively the changes observed in each patient. One system of classification based upon objective criteria which is currently widely employed by those with special interest in rheumatic diseases is known as the American Rheumatism Association Criteria. According to this system, functional capacity is divided into four classes: Class I denotes complete function; Class II indicates function is impaired but adequate for normal activities; Class III represents

markedly limited function; and Class IV indicates complete incapacitation. In order to simplify presentation of results, in this report Classes III and IV are combined because for practical purposes both refer to patients severely limited in activity.

The percentage distribution of all patients in the different classes at the beginning of the study (Table 2) was: Class I, 5%; Class II, 60%; and Classes III or IV, 35%. After five or more years of corticosteroid treatment, the majority of these patients remained capable of their usual activity without serious restriction; less than one-half of these patients were markedly restricted in their activities due to their illness. Moreover, there was only a slight change in percentage distribution of patients in the various functional classes: Class I contained 5%; Class II, 51%; and Classes III or IV included the remaining 44% of patients. However, the patients within these various classes after treatment are not the same patients that were in these classes at the beginning. As shown in Table 2, some patients moved to an improved class. For example, 10% of the patients in Class III

TABLE 2

Changes in Functional Capacity of 183 Rheumatoid Patients
(Figures in Per Cent)

	At Beginning of Observation	After 5 or More Years Corticosteroid Treatment		
		Class I	Class II	Class III or IV
Class I	5.0	0.5	2.0	2.0
Class II	60.0	4.0	39.0	17.0
Class III or IV	35.0	0.5	10.0	25.0
Total	100.0	5.0	51.0	44.0

or IV at the beginning improved to Class II. A slightly larger number (17%) beginning in Class II worsened to Class III or IV. Many patients did not change in functional capacity.

Changes in Structure: Objective changes in structure of joints and adjacent tissues are classified by the American Rheumatism Association criteria as: Stage I, absence of change except for radiographically demonstrated metaphysial osteoporosis of the bones making up the affected joints; Stage II, slight cartilage or bone destruction; Stage III, marked joint destruction with deformity; Stage IV, marked joint destruction with fibrous or bone ankylosis. Stages III and IV have been combined in this report.

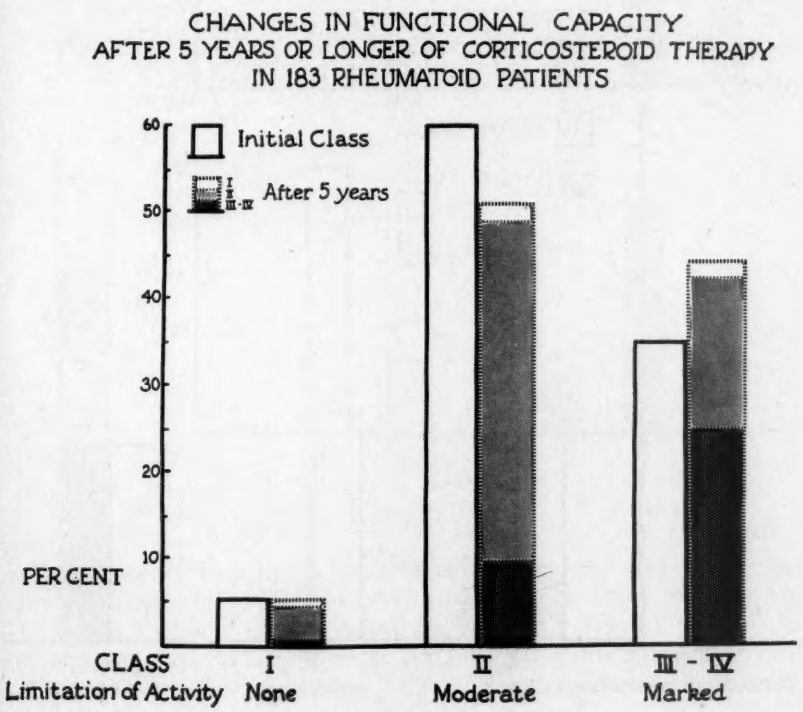
At the beginning of treatment the patients were evenly divided between Stages I, II, and III and IV. After five or more years of corticosteroid treatment only 6% were in Stage I and only 17% were in Stage II while 77% were in Stages III or IV. These striking differences indicate progression of disease, resulting in increased joint damage. Only a few patients initially in Stage I remained there. Nine per cent of all patients worsened

TABLE 3

Changes in Joint Structure of 183 Rheumatoid Patients
(Figures in Per Cent)

	At Beginning of Observation	After 5 or More Years Corticosteroid Treatment		
		Stage I	Stage II	Stage III or IV
Stage I	35.0	6.0	9.0	21.0
Stage II	35.0		8.0	26.0
Stage III or IV	30.0			30.0
Total	100.0	6.0	17.0	77.0

from Stage I to Stage II; 21% initially in Stage I worsened to Stage III or IV. Seventy-six per cent of all patients who were Stage II at the beginning, 26% of the total group, worsened to Stage III or IV. It may be seen in Table 3 that no patients improved structurally. These one-way changes resulting in more joint damage in most of the patients differed markedly from the functional changes where improvement occurred in as many patients as it worsened.

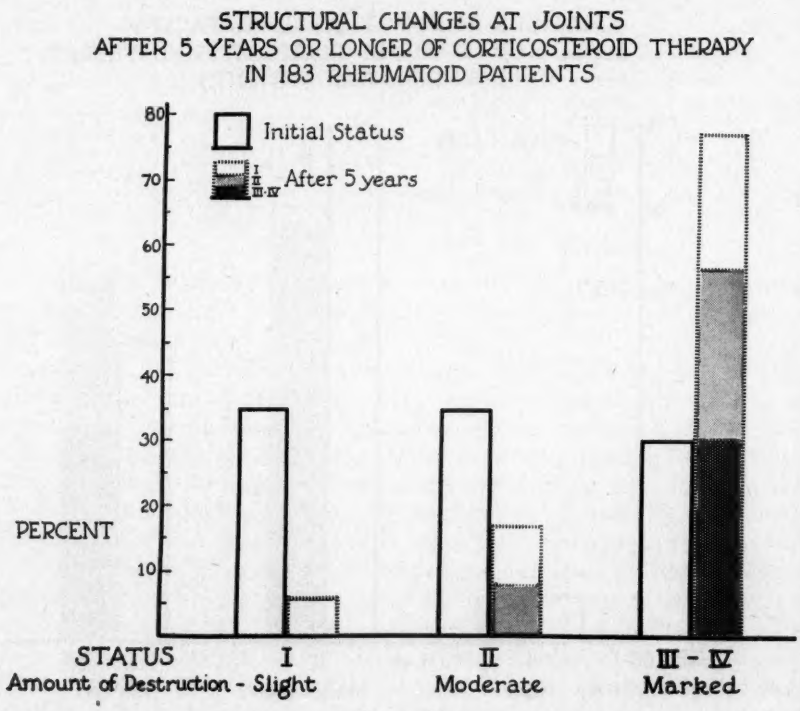


GRAPH I

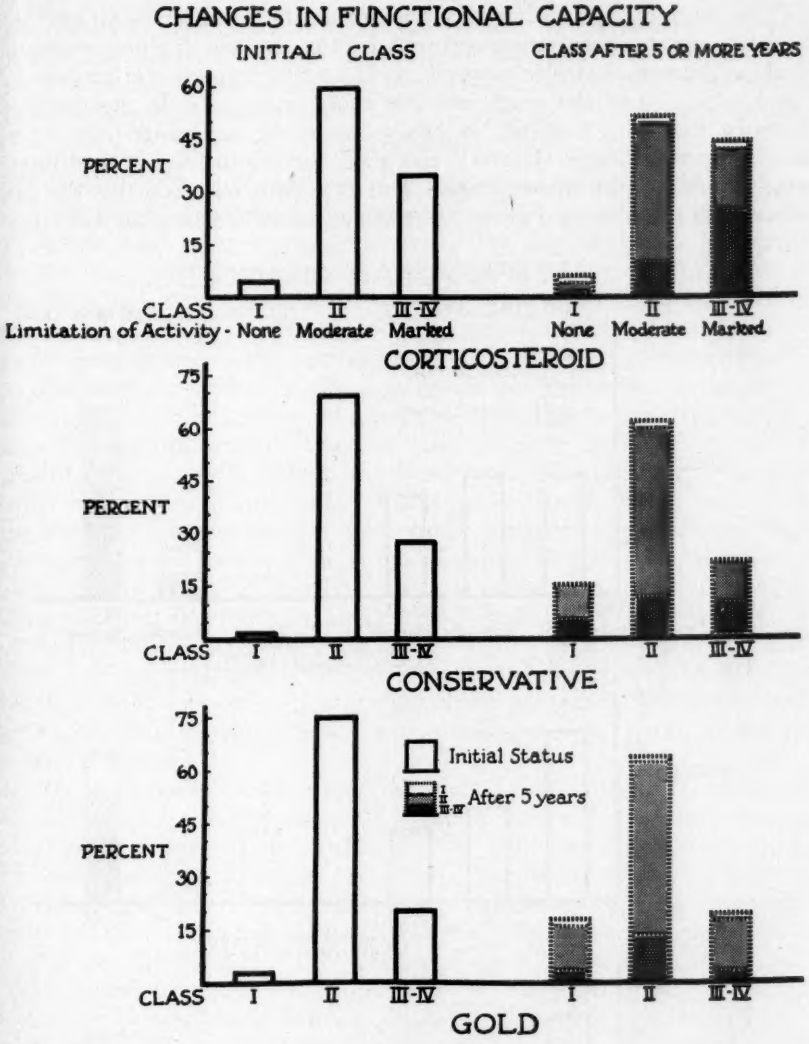
Comparison of the Results of Corticosteroid Treatment with Those of Other Types of Treatment

These changes in status of corticosteroid treated patients can be compared to change in status of two other groups of patients of the authors and their associates who did not receive corticosteroid. One group of 50 patients received only mild analgesics and physiotherapy; the other, a group of 155 patients, received gold salts in addition to analgesics and physiotherapy.

Changes in functional capacity of each treatment group are shown on Graph III with the corticosteroid groups at the top of the graph and, for comparison, the conservative and gold salt groups are placed next in order. On the left is shown the percentage distribution of patients in different functional classifications at the beginning of the study; on the right is shown the status of these same patients at the end of observation. The key on this graph indicates that patients with normal activity at the beginning are represented by open columns. Patients beginning with moderate restriction are represented by gray, and those with marked restriction of function by black columns. The percentage distribution of patients in each functional class is similar in each group at the beginning of observation. Changes in



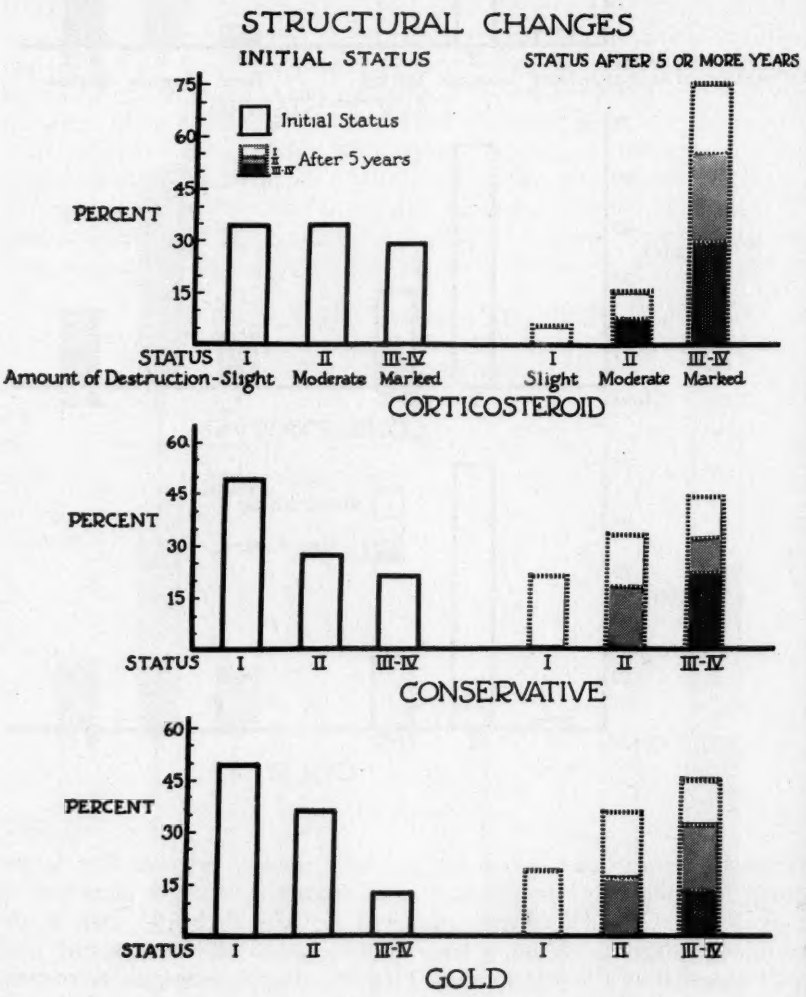
Graph II



GRAPH III

functional class in each group are generally similar, but note that in the group receiving only simple measures of treatment, a larger increment of Class III or Class IV patients improved to Class I (black) than in the corticosteroid group. Also, a larger percentage of patients receiving gold salts moved from Class II to Class I (gray) than occurred in the corticosteroid group.

The structural changes in each group of patients are shown on Graph IV. Note that structural worsening occurred in all groups and that proportionate blocks of patients shifted to more advanced stages irrespective of treatment. The top portion of the graph indicates more progression in the patients receiving steroids. However, in this group at the beginning, there were more patients in Stages III or IV and fewer patients in Stage I than there were in either of the other groups. This is a clear indication that the patients in the corticosteroid group had more advanced disease than had other



GRAPH IV

patients in the conservative and gold salt groups. Since these patients were not strictly comparable at the beginning of the study, those treated with other measures are not dependable controls for an evaluation of the effects of corticosteroid treatment.

Discussion

The object of this study was to determine the effect of prolonged use of corticosteroid upon rheumatoid disease by contrasting the patient's status at the end of five or more years of treatment with the status at the beginning. It was hoped the results of such a retrospective study would help answer two questions: (1) Are the interim benefits of increased functional capacity worthwhile? and (2) Is rheumatoid destruction retarded or prevented by prolonged treatment with a partially suppressive dosage of corticosteroid?

Results show that functional capacity was well maintained at the end of prolonged steroid treatment in the majority of patients despite striking progress of joint destruction. Function was no better in the corticosteroid treated patients than in others treated with simple measures or with gold salts. Nonetheless, maintenance of activity in steroid treated patients is particularly impressive because these patients had more severe disease than had others treated with only simple measures or with gold salts. Recall that at the beginning of treatment the anatomic changes of disease were more advanced in patients receiving corticosteroids, and that the majority of these corticosteroid-treated patients had been treated with simple measures and many had had gold salts before receiving corticosteroid but had failed to benefit from this treatment. It is clear, therefore, that the patients treated with steroid are a selected group with more severe and more "treatment resistant" disease.

The method employed of comparing the before-and-after treatment status of each patient precludes a detailed report of the striking interim changes and short-term benefits which usually occur with steroid treatment; these are well known. It should be realized that the course of different patients arriving at the same end stage (as measured by American Rheumatism Association criteria) may be markedly different. One patient may have purposeful activity with comfort for months or years with partially suppressive corticosteroid treatment, and another not receiving steroid may be unable to care for personal needs without assistance, while structural changes progress comparably in each patient so that after five or more years the end status of each patient is the same. The following summary will illustrate this shortcoming in an otherwise generally dependable method of evaluating the changes in status of rheumatoid patients.

Case Report

A young rheumatoid arthritic male could barely stand or walk after prolonged hospital treatment with simple measures and later with gold salts (Figure 1*a*). Classified Stage IV and Class III when cortisone acetate was begun, he improved

sufficiently to resume work. He has continued working for five years and has improved to functional Class II during corticosteroid treatment, which has continued for nine years. This patient has had important interim benefit despite the progression in joint destruction as shown in the accompanying roentgenograms (Figure 1*b*). Note the marked decrease in joint space of both knees, indicating cartilage destruction. Other observers have noted that the potent antirheumatic effect of corticosteroid treatment may not arrest the continued destruction of bone and cartilage.[1]

Many of our patients are similar to this illustrative example and indicate that the benefits of corticosteroid treatment are the most impressive in patients with severely impaired function and restricted activities and in others with markedly active illness which proves to be unresponsive to other available measures of treatment. As used in this study, corticosteroid improved functional capacity and provided interim relief of pain, but in our results there is no indication that the course of the disease was altered. Articular destruction may be progressive even though some objective and clinical signs of improvement are obtained with corticosteroid treatment. In the corticosteroid treated patients the continued joint destruction or worsening was comparable to the destruction observed in patients who did not receive steroids. Comparative evaluations of these changes in structure are interpreted as showing that, as administered, corticosteroids did not alter the course of the pathologic changes of the rheumatoid disease.

FIG. 1*a*. Roentgenogram of both knees at the time of beginning corticosteroid treatment (12/3/51).

FIG. 1*b*. Roentgenogram of both knees after 44 months treatment with corticosteroid (8/10/55).

This failure of partially suppressive corticosteroid treatment to reduce joint damage leads to a third question: "For the purpose of decreasing joint damage is it advisable to increase corticosteroid dosage beyond that required for partial suppression of rheumatoid inflammation?" The answer to this question depends in part upon an evaluation of these *qualified* interim benefits with the undesirable effects of the treatment as it was administered.

Serious complications occurred with corticosteroid treatment which did not occur with other treatment. For example, gastrointestinal ulceration proved by roentgenogram occurred in 19%, and pathologic fractures of osteoporotic bone in 15% of these 183 patients. Other potentially serious complications occurred: mental aberration, hypertension, severe edema, vascular change suggesting vessel inflammation, and severe infection. These complications depicted in Table 4 are different from those occurring with gold salt treatment, these being dermatitis, blood dyscrasia, and urinary changes suggesting nephritis. The complications of conservative therapy were negligible as they were not related to treatment.

During the course of five or more years among a large group of patients, of whom 80% became more than 40 years of age, some deaths are to be expected. Twenty-three deaths occurred in the 388 patients reported here (Table 5). Eighteen deaths were in the group of 183 patients who had

TABLE 4

Complicating Illnesses During Observation for Five Years or Longer of 388 Rheumatoid Patients

	Corticosteroid Therapy		Gold Therapy		Conservative Management	
	183 Patients		155 Patients		50 Patients	
	Incidence	%	Incidence	%	Incidence	%
Ulcer of stomach or duodenum	35	19	2	1		
Pathologic fracture	28	15	1	1		
Mental depression, irritability	24	14				
Hypertension	6	3				
Severe edema	5	3				
"Vasculitis"	6	3				
Severe infection	5	3			2	4
Dermatitis			63	40		
Blood dyscrasia			10	6		
Urinary abnormality (albuminuria, hematuria, ? nephritis)			5	3		

received prolonged corticosteroid treatment. Three deaths occurred among patients receiving gold salts as the special form of treatment. Two deaths occurred in patients managed without gold or corticosteroids. Careful consideration of the course of these patients' illness and the complications arising from different treatments has served as a basis for judgment as to whether or not death was attributable either entirely or in part to a complication of treatment. In this study, complicating illness sufficiently grave to produce death or to contribute to it occurred only in the group of patients receiving corticosteroid. These fatalities occurring in patients treated with corticosteroid and their principal causes are summarized in Table 6.

Of the patients treated with corticosteroid for five or more years, a total of eight deaths were due to treatment: four patients died as a result of infection uncontrolled with the appropriate antimicrobials, two died after perforation of gastric ulcer, one died as a result of suicide due to mental depression occurring while corticosteroids were being withdrawn, and another died from respiratory insufficiency associated with multiple fractures of osteoporotic ribs and vertebrae. These eight patients were judged

TABLE 5

Mortality in 388 Rheumatoid Patients Observed for 5 or More Years

Treatment Group	Patients	Deaths	% Mortality
Corticosteroid therapy	183	18	10
Conservative management	50	2	4
Gold therapy	155	3	2
Total	388	23	6

to have suffered fatality from their treatment in that their deaths likely would not have occurred had this treatment not been employed.

Four additional patients died in circumstances suggesting that prolonged use of corticosteroid was in part responsible. One patient died as a result of evisceration following emergency cholecystectomy, another from unexplained gastrointestinal hemorrhage, a third from pneumonia, and the fourth died of cachexia with terminal pulmonary embolism. The patient's cachexia was contributed to by renal insufficiency with fluid retention and uremia. In addition to these 12 deaths believed to have been entirely or partly due to corticosteroid treatment, there were six other fatalities in the corticosteroid group not related to treatment: three were due to arteriosclerotic heart disease and three to malignancy.

TABLE 6

Mortality Associated with Corticosteroid Treatment

Incidence	Principal Cause of Death
Deaths Judged to be from Complications of Corticosteroid Treatment	
4	Infection not controlled with optimal antimicrobial treatment
2	Perforated gastric ulcer
1	Mental depression leading to suicide
1	Respiratory insufficiency due to multiple fractures of osteoporotic ribs
8 Total	
Deaths in Part Due to Complications of Corticosteroid Treatment	
1	Evisceration following emergency cholecystectomy
1	Gastrointestinal hemorrhage from undetermined site
1	Pneumonia
1	Cachexia with pulmonary embolus (coexisting renal insufficiency with uremia and fluid retention)
4 Total	

Three deaths occurred in the group treated with gold, one due to arterionephrosclerosis and pyelonephritis leading to renal insufficiency, one due to arteriosclerotic heart disease, and the third due to an undifferentiated multisystem connective tissue disease. There were two deaths among the patients managed conservatively, one from thromboembolism with gangrene, the other from malignancy. Treatment neither caused nor contributed to these five deaths.

Because of the greater severity of the rheumatoid disease in the corticosteroid group, the patients treated with conservative measures and gold salts are not dependable controls for the corticosteroid group in respect to mortality analysis. Nevertheless, it is probable that the increased mortality of the corticosteroid group is due largely to their treatment, because similar

severe complicating illnesses occurred in other patients who received prolonged corticosteroid treatment. These patients are not included in this statistical evaluation because they had not used these drugs for as long as five years. Some of them became seriously ill with gastric or duodenal ulceration, pathologic fracture, or vasculitis. Deaths have occurred from complications of corticosteroid treatment of less than five years' duration. The primary causes of these deaths are similar to those in the corticosteroid group reported herein, and have been diffuse vasculitis, peritonitis caused by rupture of a diverticulum of the colon, and staphylococcus aureus septicemia.

The potential severity and frequency of these effects of treatment are startling even though the vast majority of these patients using corticosteroids were enabled to continue in their activities as they had five or more years previously. Surely it would be undesirable to contribute additional hazards to these complicating illnesses by increasing corticosteroid dosage in the hope of favorably altering the course of the rheumatoid disease.

This study lacks dependable controls, as has been shown. The differences in the initial status of disease in patients in the three groups are such that, although meaningful comparison can be made, one group is not a completely dependable control for the others. Also, comparison of these data with published reports is not satisfactory because of differences in the criteria used as bases for the beginning and end stages, and other differences in the methods of corticosteroid treatment.[2-4] The interdependence of these different methods of treatment and their results in other studies are forewarning that the results in this study and their interpretation cannot be separated from the methods of corticosteroid treatment used. With this reservation, this report can be the basis for predictions concerning group response to corticosteroid therapy, but not for predictions concerning individual patient response.

The incidence and severity of complications of treatment, and the number of deaths attributable wholly or in part to the use of corticosteroids are striking. In the hope of defining more clearly the significance of these undesirable effects of treatment, comment will be made upon three of the guidelines used in treatment during this first decade of corticosteroids.

In the early years after their introduction to clinical use, some but not all of the undesirable effects of corticosteroids became known. Certain differences in steroid effects, obtaining at different ages and sex for example, were learned only as studies proceeded. As this knowledge accumulated, attempts to lessen the troublesome effects led to decreases in daily dose. Indeed, in the early years of this study, larger doses of corticosteroid were used in some of these patients than would now be considered prudent. Along with these attempts to lessen undesirable effects by reduction in dosage, clinical trials of other corticosteroids were conducted with many of these same patients. The preliminary results of these trials suggested that several of the newer analogs might possess definite advantages. Thereafter, re-

peated efforts were made to determine the nature and extent of possible differences of effects of these newly prepared steroids. Thus, most of the patients in this study received several steroids over the course of their treatment, one replacing another as promising analogs became available. These comparative clinical trials employed the same, gradually enlarging group of patients, and assayed the merits of a total of seven steroids. It became clear that these drugs shared significant antirheumatic properties, the degree depending upon dosage. Therefore, it appeared that their potential for causing undesirable effects might be the only significant difference between them. For this reason, in order to contrast further the effects of these drugs, no attempts to prevent complications were made routinely, although optimal treatment was used to correct troubles when they occurred.

The foregoing explanation indicates that the information presented in this report comprises that collected over 10 years, and summarizes the additive effects of several steroids used one after another in this group of patients. These results, some beneficial, and others troublesome, cannot be ascribed to any one steroid, although differences in effect have been noted, depending upon the drug preparation and upon differences in patients. The description of the treatment "end results" in this report is the sum of an historical accounting of the experience acquired during many clinical trials run simultaneously or in series in the patients studied.

Finally, this study was undertaken to determine the status of patients with rheumatoid disease after prolonged, continuous treatment with corticosteroids. There should be no doubt now that the benefits of corticosteroid upon functional capacity of rheumatoids may be so encouraging that they may restore to these patients their reasons for living. But these benefits are dependent upon continuous treatment, and prolonged treatment is hazardous. Now, after 10 years of careful effort to obtain maximal therapeutic benefits of corticosteroids in rheumatoid patients, there are still complicating troubles and serious undesirable effects of their use. Satisfactory means of preventing some of these troublesome effects remain unknown. However, it is reasonable to anticipate that their incidence will be lowered with increasingly critical selection of patients and choice of corticosteroid and dosage, with careful use of clinical and laboratory guides, and perhaps with concurrent use of other medicinal safeguards of corticosteroid treatment.

Summary

This study describes the status of rheumatoid patients after five or more years of continuous, partially suppressive corticosteroid treatment. The partially suppressive dosage of corticosteroid was distinctly beneficial in that functional capacity was maintained in most and even improved in some of the patients. Moreover, functional capacity was maintained even though the group receiving corticosteroids included patients with more advanced disease

than were in two other groups of patients treated with other measures, without the use of corticosteroids.

However, corticosteroid treatment as administered to these patients failed to have an important effect in checking the progress of the rheumatoid disease. Joint destruction from rheumatoid disease progressed irrespective of treatment as it was employed, and the end status of patients after corticosteroid treatment was similar to the status of patients treated otherwise.

Serious complicating illness and deaths have resulted from prolonged use of corticosteroids although used in only partially suppressive dosage. These hazards need to be weighed with the capacity of corticosteroid drugs to relieve pain and aid function in order to obtain a balanced appraisal of their effects.

SUMMARIO IN INTERLINGUA

Iste reporto describe le effectos de cinque annos o plus del uso de drogas corticosteroide in 183 patientes con arthritis rheumatoide. Iste drogas esseva usate in le dosage minime ancora capace a permitter al patientes individual persequer lor activitates usual. Le magnitude del dose suppressive minime de corticosteroide requirite diurnemente variava in le curso del tractamento. Modalitates additional de therapia usate in le tractamento del patientes includeva reposo supplementari, le usual mesuras physic, dietas appropriate, e simple drogas analgesic.

In iste patientes rheumatoide, le capacitate functional esseva mantenite sin restriction in despecto del occurrentia de un progressive deformitate anatomic del articulationes. Al tempore del prime examine ante le initiation del prolongate uso de corticosteroide, 7 pro cento del patientes habeva nulle restriction functional, 56 pro cento habeva moderate restrictiones functional, e 38 pro cento habeva marcate grados de restriction. Post le prolongate tractamento con corticosteroides, le procentages in le tres mentionate gruppos esseva 5, 54, e 41, respectivemente. Tamen, le alterationes destructive del morbo continuava sin reguardo al mantenentia del capacitate functional attribuibile al effectos antirheumatic del tractamento a corticosteroide. Al tempore del examine initial, ante le tractamento prolongate con corticosteroides, iste 183 patientes esseva dividite equalmente in tres gruppos (1) con pauc o nulle destruction articular, (2) con moderate grados de destruction, e (3) con marcate grados de destruction. Post cinque o plus annos de therapia corticosteroide, le serie includeva solmente 6 pro cento con normal structuras articular e 17 pro cento con grados moderate de destruction. Habeva occurrite un augmento a 77 pro cento in le gruppo del patientes con marcate grados de destruction.

In plus, le resultatos del presente studio suggere que le essayo de ganiar plus function e de reducer possibilemente le destruction articular per augmentar le dosage de corticosteroide esserea pauco sage. Le spero initial que le effectos adverse del therapia a corticosteroides poterea esser evitate per le uso de partialmente suppressive doses se ha provate van. Octo mortes ha occurrite e es attribuibile al uso del drogas in question. Quatro altere mortes esseva possibilemente causate in parte per le uso de corticosteroides. In plus, 19 pro cento del patientes habeva ulceres gastrointestinal provate per roentgenographia, e 15 pro cento habeva fracturas de compression o alteremente pathologic in osso osteoporotic. Un plus micre sed ancora significative procentage del patientes disveloppava bizarre formas de mentation, hypertension vascular, o altere potentialmente nocive alterationes del physiologia normal. Quasi omne le patientes habeva un o plures del indesirable alterationes de apparentia que es causate per corticosteroides. Assi il es apparente que le uso de

corticosteroides in plus que le dosage suppressive minime haberea augmentate le alte incidentia de serie effectos adverse que es reportate in le presente studio.

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SPECIAL ARTICLE

THE ORIGIN OF LIFE ON EARTH AND ELSEWHERE*†

By MELVIN CALVIN, Ph.D., D.Sc.,‡ *Berkeley, California*

THE particular sequence of thoughts indicated by the title has its origin in my interest in the process of photosynthesis. It began when I asked myself the question: Which came first, the plants or the animals? This question had been answered in a variety of ways, but one can't help but wonder, as one learns more and more about the detailed mechanism by which living organisms store energy and use it, how they got started in the first place. Actually, these thoughts began long before we heard of Sputnik and all of its successors. However, the fact is that it is now becoming possible for us to know, perhaps within five years, whether there are organic chemicals on the Moon and what the genetic nature of the living material on Mars might be. (I am assuming, now, that there is some.) Within the lifetime of most of us we will know these things. It therefore becomes a much more pressing matter for us to surmise how life got here (on Earth) so as to have some clue as to what to look for in outer space. This is another source of the driving force for inquiry in this direction, and a very pressing driving force it is.

Therefore, in order to surmise what we should look for, we ought to extract some basic idea of the essential features of living material as we know it on the surface of the earth, so we can devise the proper instrument to look for it elsewhere. You can see that there are all sorts of pressures which stimulate—even compel—us to examine this subject in a very concrete and practical way, other than the much broader pressure of pure human curiosity, which is the pressure that has existed since man began to think about the nature of life.

WHAT IS LIFE?

It seems best to begin with a discussion of what the nature of living matter is and what properties we might expect to find, which had to be

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generated on the surface of the earth and which generation may, or may not, be going on elsewhere. Actually, what I am about to describe is nothing more than an extrapolation of the Darwinian idea. (It is rather impressive to find so many scientific people interested in a serious discussion of the origin of life. This would not have been the case 30 or 40 years ago. It was a disreputable subject then; in fact, it was a disreputable subject for almost 50 years—between 1870 and 1920. It is rather interesting to speculate why this heightened interest in the thinking about this subject has arisen.) Thoughts about the nature of life itself—really the first serious ones in modern times—stem from Darwin himself. You will recall that the basic contention of Darwin was expressed in the title of the Darwin-Wallace paper of 1858 which was titled "On the Tendency of the Species to form Varieties, and on the Perpetuation of Varieties and Species by Natural Means of Selection." [1] Darwin had already recognized the significance of this basic notion of a variety of living matter to depart indefinitely from its original type and to become a new species, and he also recognized the significance of a backward extrapolation of this notion.

Thus if you start out with two species, and if you accept Darwin's notion that these two species were originally two varieties of one species which, in turn, was once one of a pair of varieties turned species, you can keep going back until eventually you must come—and Darwin recognized this as implicit in his basic notion—to a point where there was only one type, or species, of living thing. Eventually one must come to a point at which what we would have called a living thing, if we were able to view it from a distance, was a variety of aggregates of matter, some of which we would call "alive" and some of which we would not. Further backward extrapolation leads to varieties of things even more primitive, none of which we would call alive.

This is the idea of a living organism developing in an evolutionary sequence of events in time. At some point, when material with a sufficient number of the desired properties had come together in a single region of space (a single system), we would call it alive. This is the concept that Darwin recognized even in his very earliest works. Shortly after the publication of Darwin's thesis another publication appeared, this time by a chemist, Louis Pasteur, around 1863. He did an experiment in which he showed definitely that no life could originate on the surface of the earth under the conditions that then existed, except that it came from pre-existing life. The Darwinian concept was completely overshadowed by the Pasteur dictum that one could not obtain living material except from living material. Therefore, no one dared think seriously that living material originated except from other living material. It came to an end at that point.

I wondered about that point—about why Darwin never did express himself explicitly on this matter—but it turns out that he did, and I found here his opinion on the origin of life, written in a letter to George Wallich in 1882:

"You expressed quite correctly my views where you say that I had intentionally left the question of the Origin of Life uncanvassed as being altogether *ultra vires* in the present state of our knowledge, and that I dealt only with the manner of succession. I have met with no evidence that seems in the least trustworthy, in favour of so-called spontaneous generation. I believe that I have somewhere said (but cannot find the passage) that the principle of continuity renders it probable that the principle of life will hereafter be shown to be a part, or a consequence of some general law. . . ."

The passage to which Darwin refers in this letter follows, and it shows that Darwin really did understand the significance of his basic evolutionary contention. This was written in a letter of 1871:

"It is often said that all the conditions for the first production of a living organism are now present, which could ever have been present. But if (and oh! what a big if!) we could conceive in some warm little pond, with all sorts of ammonia and phosphoric salts, light, heat, electricity, etc., present, that a protein compound was chemically formed ready to undergo still more complex changes, at the present day such matter would be instantly devoured or absorbed, which would not have been the case before living creatures were formed." [2]

This statement of Darwin contains all of the basic concepts which have been the backbone of most "origin of life" conjecture, experiment, and argument that have been going on during the last 15 or 20 years. The idea was rediscovered, so to speak, by Haldane in the middle twenties [3] and by Oparin in the middle thirties.[4]

Now that we have this idea of continuity, which is so clearly expressed by the backward extrapolation of Darwin's evolutionary theories, we can see that to try to pinpoint some moment in time at which (or before which) there were no living things and after which there were, is a mistake. The accretion of the variety of properties which today we attribute to living matter was a gradual evolutionary process itself, and only when a sufficient number of these properties found themselves in a single system in space did we call it alive. And this is a rather arbitrary point at which we will call a thing alive. Some believe that a thing must be self-reproducing in order to be alive; others say it must convert energy into negative entropy; still others say it must have the property of irritability; and there are a variety of other such descriptions which have been used to define living matter. Actually, it is the aggregation of a sufficient number of these properties in one system in space that gives rise to what we would today call a living organism. I shall not try to define how many of these properties are necessary, because it may differ, depending upon your point of view—if you are a chemist you have one point of view and if you are a geneticist you have another.

There is no ambiguity, of course, in distinguishing the living from the nonliving at higher levels. It is only at the primitive level that we have this difficulty, and that very fact is the result of the nature of living material, being, as it is, an aggregation of a more or less arbitrarily sufficient number of properties in one system.

I think we must leave the idea of the nature of living materials now, and go on to describe how such a system—a physical-chemical system—could have arisen on the earth, and then examine other astral bodies to see if there is any possibility (or hope) that such similar properties might have occurred elsewhere.

The Primitive Atmosphere

We know a great deal more today, I might say, about the nature of the fundamental living organism—the actual physical-chemical processes, the construction and the interaction of these molecular particles in a living organism—than we did even 10 years ago. While one can revise each time this discussion occurs as to what we must look for, there are certain rather primitive requirements which always appear. We must, somehow, devise ways and means of producing rather complex forms from relatively simple ones.

We have every reason to suppose that the primitive Earth had on its surface only simple organic molecules. If it was a reducing atmosphere (and it seems to be generally agreed now that it was), most of the carbon was very largely in the form of methane or carbon monoxide (some of it could have been carbon dioxide, but the contention now is that most of the carbon was reduced), the nitrogen was mostly in the form of ammonia, there was lots of hydrogen, and the oxygen was all (or very nearly all) in the form of water. These, then, presumably, were the primitive molecules of the primeval Earth, and from these we must now devise a way of constructing the more complex materials.

It was at this point that we first began to seek ways of doing this in the laboratory. This was the first point of contact with experiment that I, at least, was able to make roughly 10 years ago. (At that time I wasn't so convinced, nor was it so generally accepted, for that matter, that the primitive atmosphere was reduced.) We started with carbon dioxide and water to determine whether or not it was possible to make reduced carbon compounds without the presence of the photosynthetic system which we now have. We did it by using high energy ionizing radiation or by using ultraviolet light, and it was easy to show that by irradiating solutions of CO_2, water, and hydrogen, we could get reduced carbon.[5] I think that today it is a lot easier to do this type of experiment because we now believe the atmosphere to be a reduced one. To simulate a reduced atmosphere and the same kind of ionizing radiations, instead of using carbon dioxide we now use methane, and by adding ammonia, water, and hydrogen we can get a whole variety of chemicals. The first experiment with the reduced atmosphere and ammonia was done by Stanley Miller in 1953;[6] our experiment with CO_2 and water was done in the cyclotron in 1950 and we got formic acid, acetic acid, and things of this kind which are reduced carbon compounds. When Miller put ammonia into the gas mixture, he got glycine, alanine, beta-alanine, and several other amino acids.

The Time Element: I have overlooked a rather important point in the course of getting into the chemistry of evolution and that is the geologic time element which was involved. Figure 1 gives some idea of the time scale that we have to deal with. You can see that we have ample time to do all the things which I am going to describe. We have, roughly, from two to four billion years. This not only gives some idea of the time scale, but the basic idea of the place of chemical evolution in the scheme of things is shown quite clearly. Roughly five to six billion years ago the Earth was formed and slowly hardened into its present shell. Right after the formation of the crust of the Earth, the processes of increasing the com-

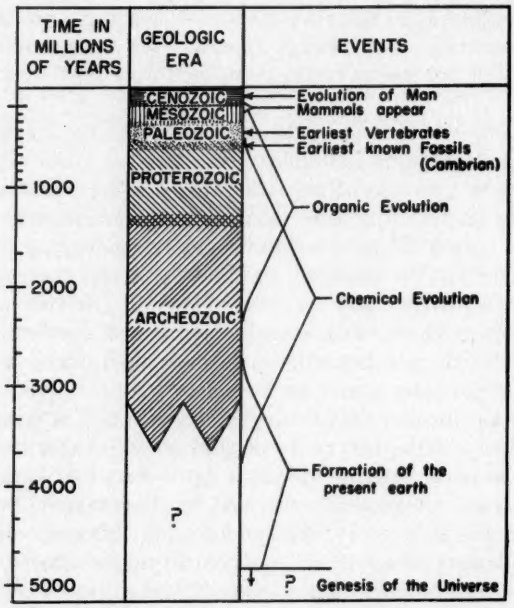


FIG. 1. Time scale for total evolution.

plexity of organic chemical formation began, and this long span of time (including the Archeozoic and Proterozoic geologic areas) I have called "chemical evolution," that is, the period of time during which chemicals were transformed from relatively simple, primitive molecules into the very complex ones which eventually, somewhere in the middle of this period, evolved into a complex system which had enough of the properties we usually attribute to the living organism so that we are willing to call it alive. At this point, organic evolution began (Darwinian evolution). This paper will be concerned principally with the part of the time scale which I have labeled chemical evolution, for which we have no fossil record on the surface of the earth.

Primitive Chemicals, the Primeval Atmosphere, and Random Organic Synthesis: Figure 2 shows the primitive chemicals with which we had to deal and which had to be converted into the more complex ones which today represent the metabolites and structural elements of a living organism. I mentioned a moment ago that with carbon dioxide, water, and hydrogen we could make formic acid, and with methane, ammonia, hydrogen, and water we could make many more complex materials, such as glycine, succinic acid, et cetera. You will notice that all of these materials are today important simple metabolites through which carbon skeletons are very often rearranged by the present-day living organisms. These materials are also the very first molecules that show up in a random synthesis, that is, a synthesis which depends primarily upon the ripping apart of existing simple molecules and the resulting fragments falling together into metastable struc-

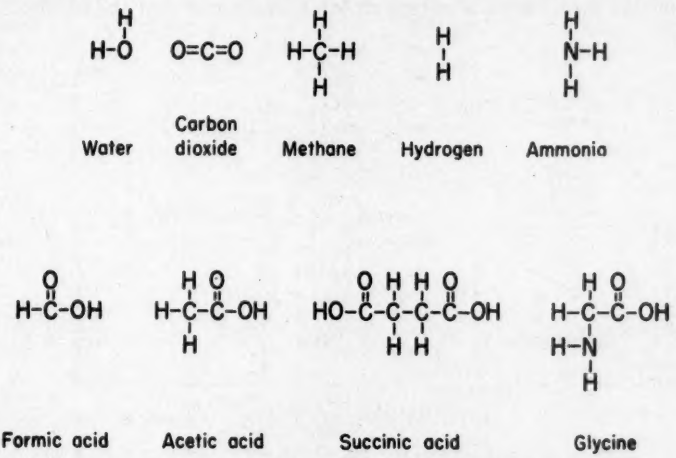


FIG. 2. Primeval and primitive organic molecules.

tures, i.e., metastable under the very highly ionizing conditions I have described. A few of these compounds are caught in this metastable condition and can be used for further construction.

This random synthesis, as you can see, could go on for quite a while, but eventually enough of the carbon would be in these forms so that the very same processes which took these precursor molecules apart would start ripping the products apart. A few of the molecules would become still more complex, but some of them would revert to more primitive forms. So, we have to introduce some kind of selection process at this point which will permit the selection of those molecules which have some self-perpetuating survival value. This process is very familiar to the chemists, i.e., chemists have recognized its existence, and we have called it autocatalysis. Any product which has a catalytic function in its own formation will, naturally,

help to transform the raw materials to suit itself. There is nothing profound about this idea to a chemist; it seems rather primitive, but it is a rather important concept. In fact, it is the very concept of self-reproduction used by the biologists, if you want to extrapolate it that far.

Evolution of Catalysts

The catalytic properties of the primitive materials may themselves have been rather simple. For example, in Figure 3 we show how we can change those catalytic properties. We are presently discussing the ability of a simple, hydrated ferric ion to decompose hydrogen peroxide and give water and oxygen, or to act as a peroxidase (oxidation catalyst). Simple aqueous ferric ion has a catalytic activity expressed by the number 10^{-5}. If, however, we surround that iron atom (iron ion) with a suitable organic grouping—in this case, haem, a tetrapyrrole—it turns out that the catalytic ability

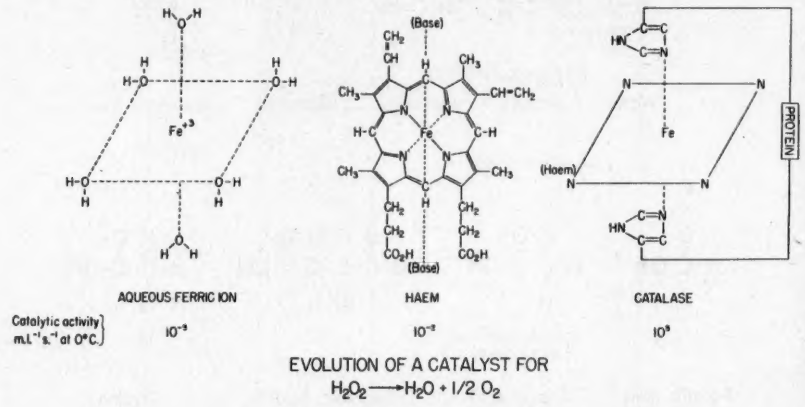


Fig. 3. Evolution of a catalyst.

of that iron in this very same process has been enhanced by a factor of 1,000, reaching 10^{-2}. If we build the heme into a still more complex structure with protein around it, we can increase the catalytic ability by several more powers of 10. The purpose of this figure is simply to show that the catalytic power residing in the iron for a simple reaction can be enhanced by the environment in which the iron is placed.[7]

The question is: How can this come about in a natural, evolutionary way without having someone who knows all this decide that it should be so? The answer lies in autocatalysis and self-selection, and Figure 4 shows how one of these things might conceivably occur. Here you have a sequence of reactions, leading from the compounds which, we saw, were randomly synthesized by radiation (succinic acid and glycine) to the porphyrins. The sequence of reactions involves simple condensation, followed by decar-

boxylation and another condensation (a double condensation, really) followed by a series of oxidation steps, leading finally to the tetrapyrrole. If any of these steps is catalyzed by iron and if the iron porphyrin structures turn out to be better catalysts for any of these steps than the bare iron itself, you can see that once this process begins (as it would have begun it here by random synthesis and condensation), an auto-selection of this sequence would enhance the transformation of the succinic acid and glycine into delta-aminolevulinic acid and finally into the porphyrin. Already there is evidence that in the presence of iron and oxygen (or iron and water, for that matter) and ionizing radiation or even ultraviolet light, one can actually synthesize small amounts of porphyrin non-enzymatically, that is,

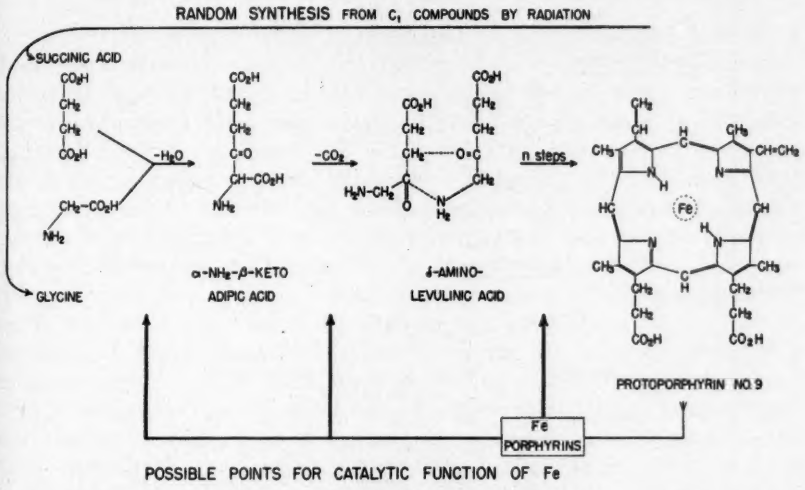


FIG. 4. Biosynthesis of porphyrin and the evolution of the catalytic functions of iron.

by the primitive catalytic abilities of the iron and the iron porphyrins themselves.[8]

MECHANISMS OF ENERGY TRANSFER

One other aspect of the living organism which is very often alluded to, the ability of the living organism to transfer energy, is frequently considered to be one of its primary properties. It is often described in terms of the ability of the organism to transform chemical energy from one form into another, usually from the form of sugar into the form of pyrophosphate linkage. This is what most organisms are able to do today. The question arises: How does that come about? Here, again, I want to call upon the primitive catalytic abilities and show how this development of energy coupling systems might develop toward a system that might actually obtain

today. Figure 5 shows how the energy involved in the oxidation of iron (the removal of an electron from ferrous iron to make ferric iron), or some part of it, may be used to condense two phosphate linkages to form a phosphoric anhydride linkage—a pyrophosphate bond. This suggestion of the ability of iron to do this for a variety of reasons was made six or eight years ago, and we actually tried using bare, or hydrated, iron ions to synthesize pyrophosphate by oxidizing iron in the presence of orthophosphate to see if we couldn't produce pyrophosphate.[9] We were not able to demon-

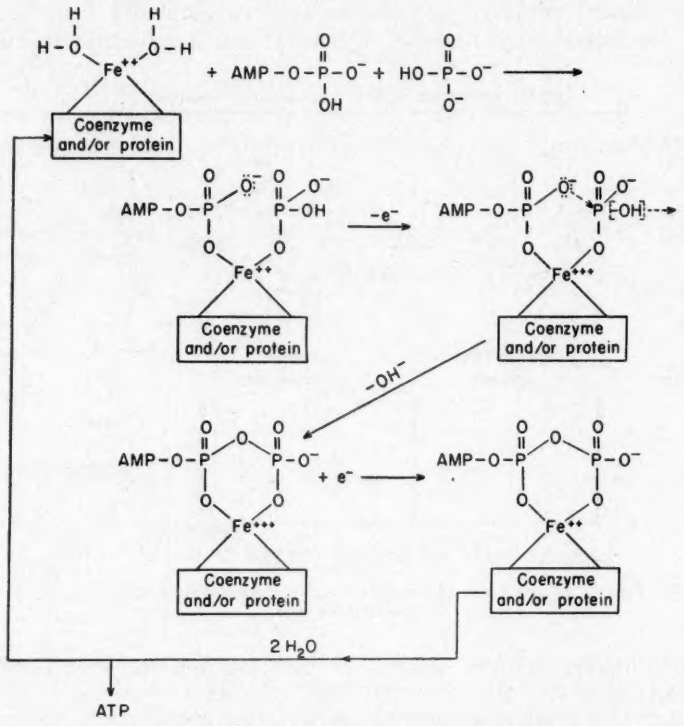


FIG. 5. Pyrophosphate energy storage.

strate the formation of any pyrophosphate by simply oxidizing ferrous iron with air in the presence of orthophosphate.

I just learned recently, however, that one of my former colleagues and present associates, Dr. John A. Barltrop, at Oxford, has indeed succeeded in doing this, at least tentatively. The way he did it was by putting a proper organic construction around the iron. Instead of using the bare iron, as we did, he used an iron porphyrin, and he was able to show the appearance of pyrophosphate when that ferrous protoporphyrin was

oxidized to ferric protoporphyrin in the presence of phosphate.[10] I trust that this will turn out to be a confirmed and successful experiment, because it does give us a clue as to how iron porphyrin evolved and how the energy of oxidation of iron can be stored during the formation of pyrophosphate.

We have now discussed several aspects of the generation of living material. The first was the conversion of simple compounds into more complex ones in a random fashion; the second was the auto-selection by which only certain compounds were formed from the precursors, which have some autocatalytic function; and the third was the way in which the energy conversion and storage process might have had its beginning.

From Chaos to Order: Molecular Crystallization

All of the above aspects of generation of living material have been discussed in terms of molecules in random solution—molecules presumably contained in water but not oriented with respect to each other, merely dissolved and randomly moving around in solution. We know that another aspect of a living organism is the fact it is *not* random—it isn't just a big bag full of molecules behaving randomly. Whenever you look at a living organism from its outside (the whole man, in other words) or into its innermost part (whether it be a man or a microbe), you find that it is an organized structure; it is not simply a sack of catalysts and their substrates. A living organism is a highly organized structure in which all of the elements are related one to another in a rather specific way. This, to me, calls to mind the idea of crystallization which may give rise to order, and which makes us wonder how the order arose in the first place in living organisms.

The order of a crystal resides in the nature and symmetry of the molecular interaction which, in turn, is a property of the structure of the molecule itself—what its shape is, what its force fields are, et cetera. So the nature of the order is really built into the molecule itself. We must, therefore, look into the construction of the molecules themselves to see if there is anything in them which might give rise to the kind of order we see in living things.

Protein Structure: This probing is not difficult to do. There are three kinds of macromolecules upon which the structure of living organisms is based. The first, and possibly the most important of these, is the protein. The proteins, of course, are made up of amino acids in polypeptide linkage, the secondary structure being the helical structure and the tertiary structure being the various ways in which the helix itself is folded. We already know that the helical structure is at least partly dependent upon the particular geometry of the peptide structure itself, and this gives rise to the helix. This, in turn, when it is properly packed, will give rise to actual visible, macroscopic structure.

In fact, in just the last year or so, another biochemist, S. W. Fox, has been doing experiments on the conversion of the simple amino acids into

proteinaceous, or proteinoid, material under nonbiologic conditions, that is, under what he calls prebiologic conditions. What he did was to take a mixture of from 18 to 20 amino acids and heat them in molten glutamic acid. In so doing, he was able to get the amino acids to hook up together, one to another, to make polypeptides of rather large structure (3,000 to 10,000 molecular weight). He was able to reduce the temperatures at which he had to perform this experiment by adding some polyphosphate. When he puts polyphosphate into the reaction mixture, he finds he can get proteinoids out of mixtures of amino acids at temperatures of around 70 to 80° F. and

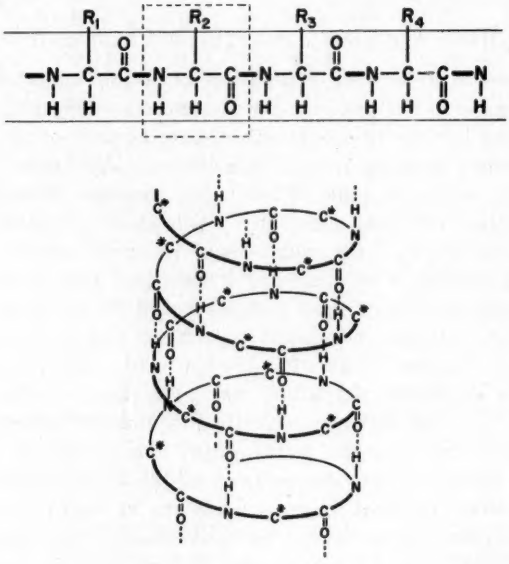


FIG. 6. Protein structure.

these proteinoids are materials of relatively high molecular weight. Furthermore, if he lets the proteinoids cool out of a clear aqueous solution, they begin to assume various shapes and forms which, to Fox at least, have the appearance of *cocci,* and they behave in some physical respects as if they were spherical organisms or bacteria which have a spherical shape.[11-13] Already, just in the proteinoid material itself, one can begin to see that structural features are built into the molecular structure.

The other aspect of the protein contribution is what it does to the catalytic properties of the elements with which it may be associated. Both

aspects depend upon the protein construction, which is shown in Figure 6. The dotted square surrounds these amino acids, of the type which we can make by random synthesis, and when the amino acids are hooked together by dehydration (the removal of a water molecule between the acid and the amino groups), we get peptide linkages. When there is a long chain, because of the tendency of the hydrogen on the amide nitrogen to form a bond with the amide carbonyl of a suitably placed peptide group (three residues, more or less, are removed from the hydrogen), we get the well-known alpha-helix formation which is a built-in element of order—built into the polypeptides because of the very nature of the structure of the peptide linkage.

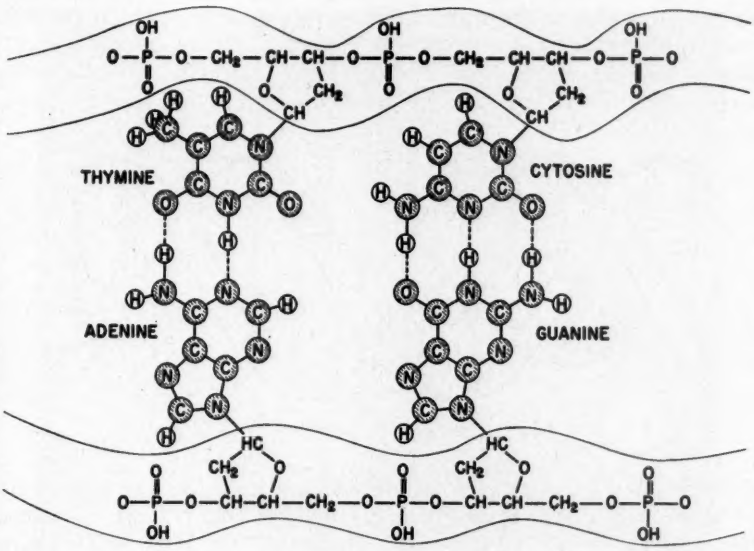


FIG. 7. Drawing of molecular components of desoxyribonucleic acid.

Nucleic Acid Structure: Another major macromolecule of living organisms, and one which we have heard a great deal about in the last decade, is the genetic material itself, the nucleic acid which presumably carries the information which the living organism uses to reconstruct itself. The structure of nucleic acid also has built into it certain elements of order. Figure 7 shows that nucleic acid is made up of a group of four bases (adenine, thymine, guanine, and cytosine) which are held together, in pairs, by hydrogen bonds. These bases are, in turn, attached to the ribose, or desoxyribose, sugar. The desoxyribose sugars are each held to their neighbors by phosphate linkages. Imagine the nucleic acid as being made up of a series of flat discs, along the edges of which are these ribose phos-

phate ribbons. If you take the two ribose phosphate ribbons and twist them into a double spiral you get the kind of structure shown in Figure 8, which is pretty certainly a basic structure of the desoxyribonucleic acid (DNA) molecule.[14] The ribose phosphate ribbon is on the outside and the hydrogen bonds are in the middle holding these disc-shaped pairs of molecules together, with one pair on top of the other, flat side on. This is intrinsically a stable kind of molecular arrangement—a sort of molecular crystal—which corresponds to the stable type of packing for unsaturated aromatic type molecules, or *pi*-molecules, here represented by these pairs of bases. The nucleic acid also represents a type of order which is built into the molecule, and results from the structure of its component parts.

The question has arisen, and is now in the very forefront of biochemical study, namely, what is the relationship of the order of bases in the DNA helix, which presumably contains the information for the reproduction of an organism, and the construction of the protein shown in Figure 6? This is a very active field of investigation at the moment. How does the nucleic

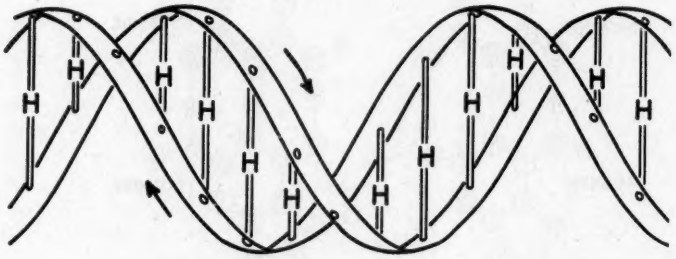


FIG. 8. Double helix model for DNA.

acid determine the structure of the protein, and how does the protein build the nucleic acid? Which came first? In evolutionary terms, how could nucleic acid evolve without protein? How could the relationship between nucleic acid and protein have arisen?

One school of thought emphasizes that the protein must have been developed first.[13] Another group, the geneticists, says that the essence of the living organism is the self-reproducing nucleic acid (DNA) molecule.[15] The question of how they got to know each other is not very clear and is, as was stated earlier, the subject of the immediate investigation.

It seems to me to be very likely that the two things arose in the evolutionary scheme side by side. The random synthesis which is shown in Figure 2 shows none of the nucleic acid particles; it shows only the amino acids, which are on the way to proteins. Until now, there hasn't been any real evidence that the nucleic acid components, the bases—adenine or guanine, for example—can be made by random synthesis. No one had yet demonstrated this. (We will return to this later.)

Relationship between Visible and Invisible Structures: In this stage of the story we must now put these various structural elements together to form the ordered array which one finds in the living cell, and I think that one can call upon the structural features of the molecules themselves, in general, to give rise to the macroscopic order that one sees. Figure 9 is an electron microscope photograph of tobacco mosaic virus (TMV) and shows the clear, clean, visible structure of the tobacco mosaic virus, which is made up of both nucleic acids and proteins. Figure 10 shows what happens if you take the nucleic acids and the proteins of the tobacco mosaic virus apart and then dump the proteins back into the solution under such conditions that the proteins will reaggregate. You will notice that the proteins reaggregate in

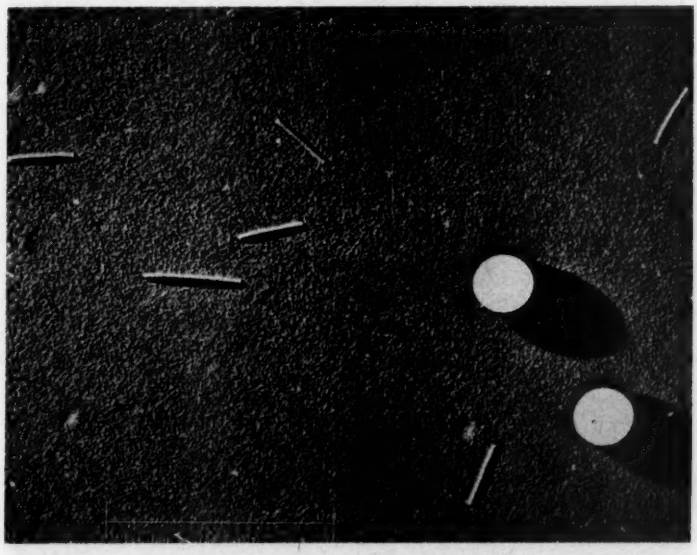


FIG. 9. Native tobacco mosaic virus (TMV).

long, rod-shaped particles, just as in the TMV itself, but the length of the particles varies. The nucleic acid is missing, but enough of this structural element is built into the protein so that it reaggregates in a crystallization phenomenon, giving something which looks very much like the structure of the intact virus. If, however, we put the protein and nucleic acid back together again, we find (Figure 11) that the tobacco mosaic virus particles come out at about the right length.*

It is quite clear, therefore, that both of these structures (the protein and the nucleic acid) are required to give the right total structure for the TMV particle. An interaction occurs between these two elements to bring about

*The photographs for Figures 9, 10, and 11 were kindly supplied by Professor Robley C. Williams of the Virus Laboratory.

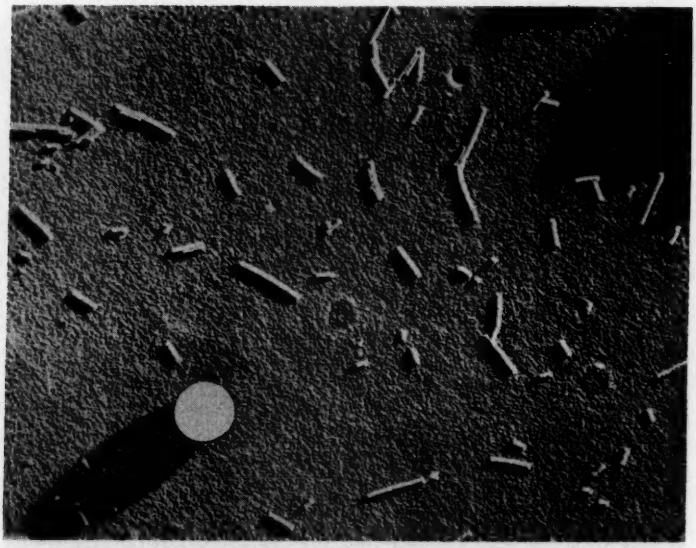


FIG. 10. Repolymerized TMV protein.

the final construction. This is nothing that has to be done by some "unknown force." These are, if you like, molecular crystallization phenomena.

There is, of course, an area of unknown, noncrystalline (colloidal), surface chemistry acting for the construction of structural features, in which we

FIG. 11. Reconstructed TMV protein and ribonucleic acid.

are not as fully educated as we ought to be. This is one of the areas in which we should do more work. However, I don't think it will be found too difficult to make the next step from the structural features which we have outlined as intrinsic in the molecular structure itself to the construction of the cell.

Life on Other Planets?

With this information as a background, we can proceed to the next step. We have gone through chemical evolution right up to the point where we have formed a primitive organism of some sort. From here on the Darwinian selection mechanism can take over and I shall go no further with this aspect of the discussion.

The next idea I want to take up is the application of this type of reasoning to the question of whether we are likely to find that similar events have occurred elsewhere than on Earth.[16] What is required for this sequence of events to occur? A certain temperature range, a certain composition of the atmosphere, and a variety of other things, all of which are now definable. The sequence of events occurs because of the nature of the carbon atoms, nitrogen atoms, hydrogen atoms, et cetera, giving rise, as they do, from methane to acetic acid, to formic acid, to malic acid to glycine, and so on, which, in turn, give rise to proteinoids and to the nucleic acid types of molecules, and thus build up in structure the order of living organisms and the interaction of molecules of the type required. All of this action hinges, in fact, upon the nature of the elements with which we are dealing, namely, carbon, hydrogen, nitrogen, oxygen, iron, phosphorus, and the rest.

Given a set of Earth-like conditions (physical and chemical), we can expect this sequence of events to occur. The question is: Are there any other places where this set of conditions might obtain? Here we must turn to the astronomers, and they tell us that in our solar system the only places where we are likely to find a set of conditions which would correspond to the ones which we have just described are on our two neighboring planets—Venus (on the inside) and Mars (on the outside)—and that there is some chance that this set of conditions might be closely enough approached on each of these two planets so that a similar sequence of events, contiguous with the ones we have just described, could have occurred and might even be occurring today.[17] In fact, there is some evidence that on the surface of Mars there are organic compounds which vary with the geography of the surface and with the seasons.[18] However, our ability to observe is still so limited that we can just barely make out, say, a carbon-hydrogen frequency in the reflection spectrum of Mars. We would like to be able to do better, and I think we will, within the matter of a few years. (There are other uses for high-flying vehicles and satellites besides looking down—you can look up!)

Meteorite Experiments: Another type of experiment we could do would be to go out into space and collect bits of these various planets and asteroids,

and bring them back to Earth to see if there any organisms in them, or, if not organisms, anything that might have constituted the prebiologic environment we are talking about. Unfortunately, we can't do so yet—it will probably be more than five years before we can do that. But there are available to us materials from those regions of the solar system which should give us some information about what is out there. These are, of course, the meteorites. We can't place an order for meteorites. We have to take them when and where they come, and that isn't very frequent; and what is more, they get put into museums and you can't get them out. (I don't blame the museum keepers. Actually, if they gave the meteorites to everyone who asked for them, there would be none left. So, they do not show an unreasonable reluctance. It is just too bad there aren't more meteorites to be had!)

In any case, we were able to get samples of meteorites, one from the Smithsonian Institution (Murray) which fell in 1951, and one from Paris (Orgueil) which fell in 1864. These meteorites contain carbon, which is the main reason for looking at these particular ones. Unfortunately, meteorites do not contain much carbon; about 2% of the total weight of a meteorite is carbon, and of that 2%, a large fraction of the carbon is not extractable. The carbon is not in the form of carbide but is perhaps in some other form which is not extractable under the mild conditions we must use.

From these two meteorites one can extract, with water, an appreciable fraction of the carbon. One of them (the Orgueil) contains salt which is mostly magnesium sulfate, and from the other (the Murray) we extracted a salt which is mostly calcium sulfate. The carbon content of these water extracts is also not the same for the two meteorites. However, both meteorites show ultraviolet and infrared absorbing material, which might lead one to believe that a wide variety of compounds is present in these water extracts, including hydrocarbons and heterocyclic bases. Figure 12 shows the infrared absorption found in a carbon tetrachloride extract of the Murray meteorite. A clear carbon-hydrogen absorption ($\sim 2{,}900$ cm.$^{-1}$) is evident and there is a carbonyl absorption, as well ($\sim 1{,}725$ cm.$^{-1}$). This is a rather complex material (a mixture of many things). Figure 13 shows the ultraviolet absorption of the water extract as a function of pH. You can see that there is a pH-sensitive absorption band right where cytosine absorbs; it behaves very much like a cytosine type of absorption.[19] I don't think this is cytosine; it's not pure, for one thing—it is a mixture.

The meteorite analysis is proceeding. Unfortunately, we don't have enough of either one of these meteorites to give a definitive statement of the construction of this cytosine-like material contained in the meteorite. I can only tell you the general character of the compounds that are found in the meteorites.

I might say that we have found no amino acids in the aqueous extracts of the meteorites. This is harking back, now, to the question of which

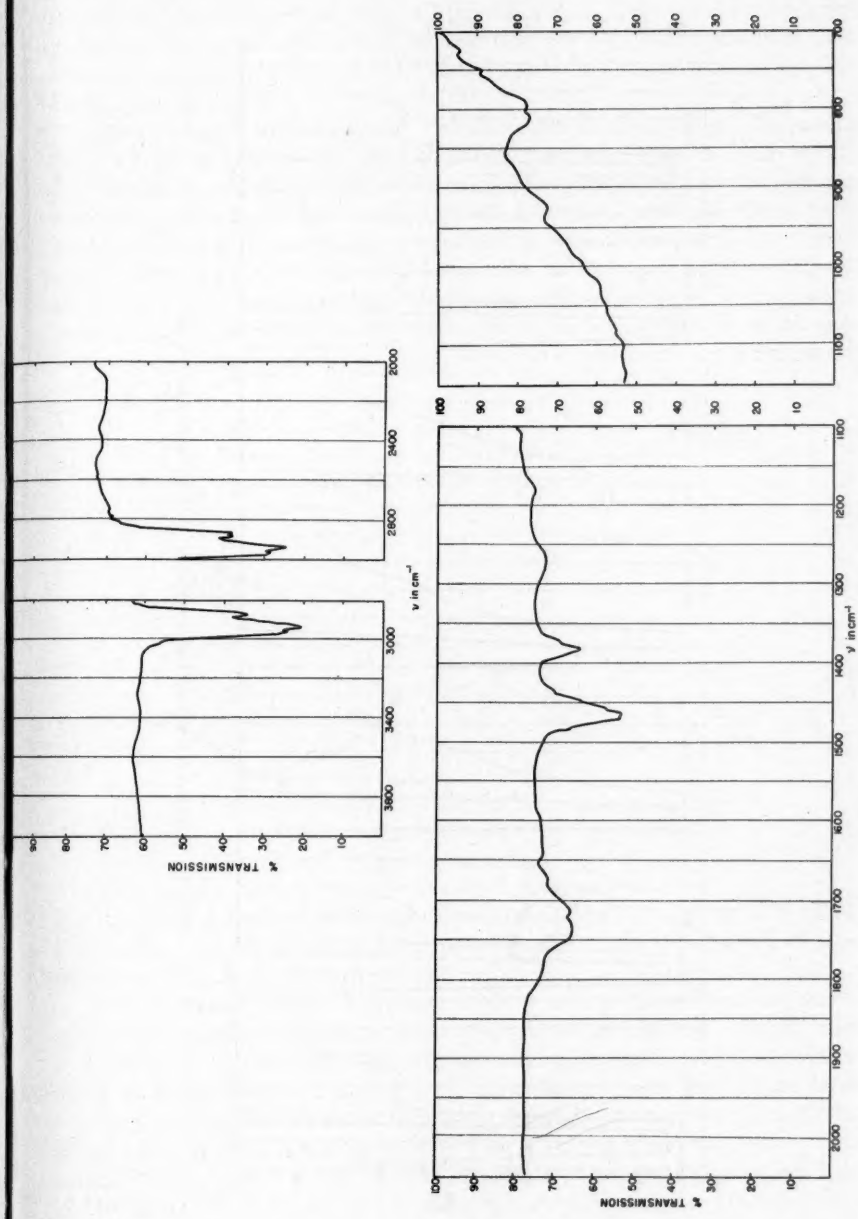


FIG. 12. Infrared absorption spectra of extract from Murray meteorite.

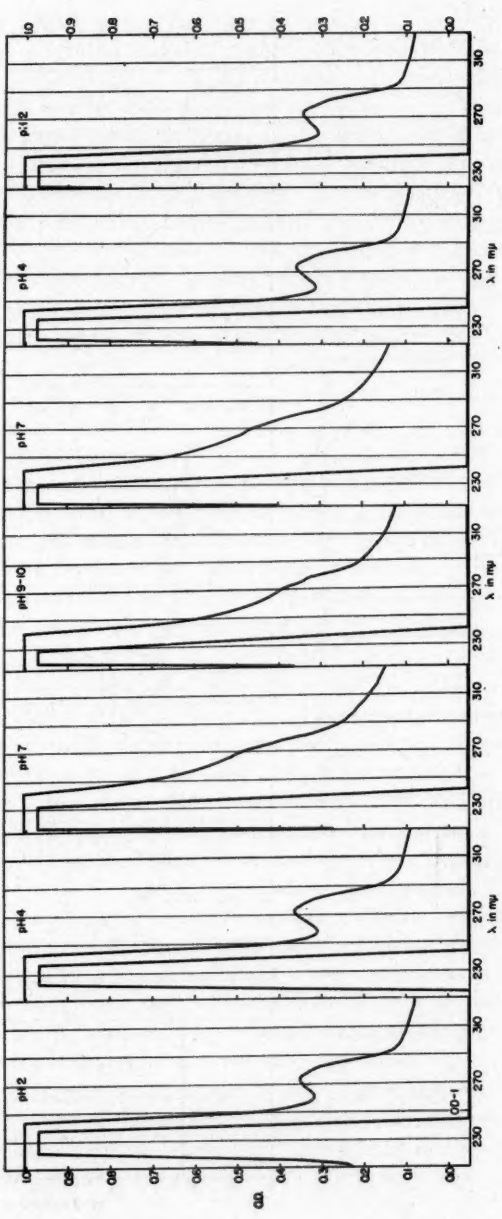


FIG. 13. Ultraviolet absorption spectra of Murray meteorite extract.

came first, protein or nucleic acid. I point out that neither of the meteorites yielded amino acids which could be detected in the extracts, although they both showed this type of ultraviolet absorption as well as a hydrocarbon-like material in the infrared.

Amino Acid Synthesis under Primitive Earth Conditions: The other thing I want to call to your attention is the fact that there is much in the way of organic material in the solar system and interstellar space that we can recognize. It is in the form of light emission from, for example, the comets. There is much carbon-hydrogen emission and lots of cyanide in the comet tails. This is a rather important observation, as the experiments of Miller [6] attest. He irradiated methane, ammonia, and water and got glycine, alanine, and a few other amino acids. It turns out, however, when you look at it carefully (and we have done the same experiments here) that these

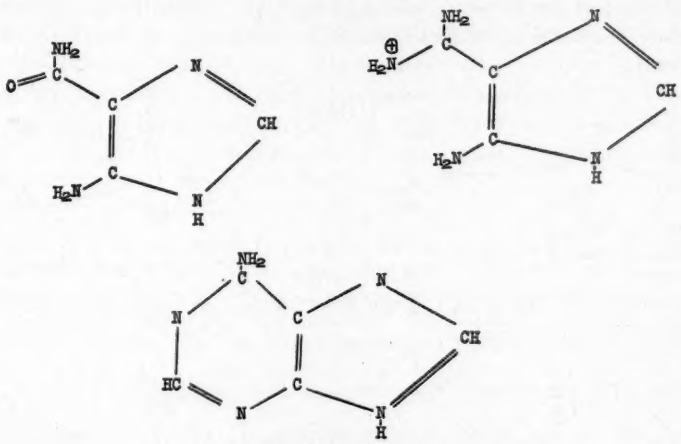


FIG. 14. Adenine.

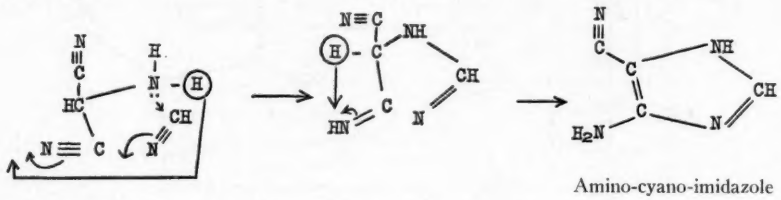
amino acids represent an extremely small fraction of the amount of methane that has been converted to organic material—less than 1%. Most of it is something else, as yet undetermined.

The mechanism of the formation of these amino acids, however, seems easy to understand, although again it is subject to uncertainty. Presumably it is an HCN addition onto an aldehyde in the presence of ammonia that forms an amino acid—a Strecker type of synthesis. This means that when you put ionizing radiation through methane and ammonia you get HCN. It turns out that HCN and ammonia make a very sensitive mixture. This sensitivity has been demonstrated by a number of people, but most recently by Oró et al.[20-23] Oró was able to show that mild heating ($> 100°$ C.) of a mixture of ammonia and HCN (approximately 1 N equivalent ammonium cyanide) produces, in addition to a large amount of black polymer,[24] identifi-

able compounds in small amounts. By extraction and chromatography, Oró was able to identify the two imidazoles and adenine shown in Figure 14. It is interesting to note that adenine is isomeric with a pentomer of HCN, that is, it has the empiric formula $(HCN)_5$. The two imidazoles can be formulated in terms of a sequence of self-additions of HCN and they might very well be intermediates on the way to the formation of adenine.

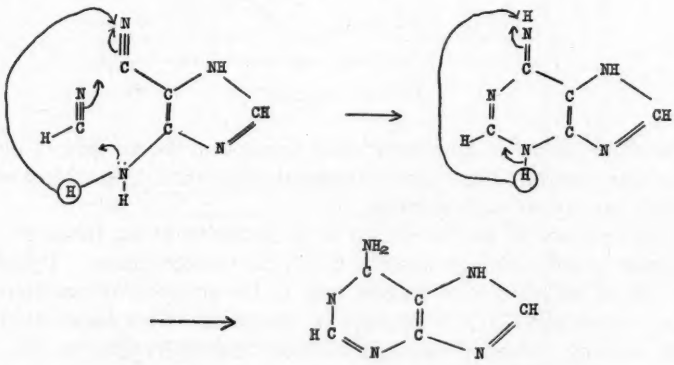
In fact, two HCN additions across a third to produce the known but unstable trimer, aminomalonitrile,[25] could be followed by an addition (of the

inverted type) of the resulting amino group across a fourth HCN to produce the amino-cyano-imidazole which would be the parent of the two that have been found:



Amino-cyano-imidazole

A final addition of the amino group thus formed across another HCN with ring closure leads to adenine.



Adenine

We ourselves have done a bombardment experiment, starting with a mixture of methane, ammonia, hydrogen, and water, and found a small

amount of amino acids of the general distribution that Miller reported. In addition, however, we found a large number and variety of other compounds on the paper chromatogram which we have located, by using radioactive methane, but which as yet are unidentified. It is not at all unlikely that some of these will turn out to be aromatic types of heterocycles, and we are thus brought to the view that both the heterocyclic compounds and the amino acids may have been formed in the very earliest stages of chemical evolution.

Conclusion

It thus appears that two separate functions (the catalytic development of the proteins and the code development of the polynucleotides) arise and grow simultaneously. This could account for the present-day close relationship between these two substances. It remains for us to develop both kinds of observations, to explore, as the biochemists are doing, the present-day mode by which the code contained in the polynucleotides is translated into the chemically versatile protein, and, approaching from the other direction, to examine the modes of chemical reactions which might lead to structural interrelationships between the purine and pyrimidine bases, their polymerization into polynucleotides, and the generation of amino acids and polypeptides.

Summario in Interlingua

Es describite—a base theoric e experimental—le synthese de relativemente complexe moleculas organic ab methano, ammoniaco, aqua, e hydrogeno per mechanismos de ionisation e mechanismos a radicales, actuate per radiation a alte energia e ultraviolette e discargas electric. Es monstrate que le moleculas que tende a formar se sub tal conditiones aleatori es precisemente le moleculas que in nostre dies es le componentes structural in le reconstruction biologic de materiales organic. Tal moleculas es le amino-acidos, le simple acidos carboxylic e hydroxylic, le purinas, pyrimidinas, etc.

Le apparition de systema e ordine inter tal moleculas aleatori es le consequentia de duo fortias, autocatalyse e crystallisation. Iste secunde es particularmente importante in le apparition de altemente efficace structuras macromolecular e arrangiamentos structural del typo eminentemente characteristic de organismos vivente in nostre dies.

Es signalate punctos de contacto inter iste theorias e experimentos laboratorial. Es describite le areas in que confirmation ha essite obtenite; es definite le areas in que ignorantia persiste e in que experimentation additional es requirite. Un prime passo in le effectuation de tests con iste prebiotic syntheses organic in altere corpores celeste ha essite facite in le forma de examines del materiales organic que se trova in meteorites. Le natura del structuras representate in ille materiales es signalate.

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CASE REPORTS

HYPERCALCEMIA OF MALIGNANT DISEASE: CASE REPORT AND A PROPOSED MECHANISM OF ETIOLOGY *†

By GERALD E. STONE, M.D., CHRISTINE WATERHOUSE, M.D., F.A.C.P., and ROGER TERRY, M.D., *Rochester, New York*

HYPERCALCEMIA, as one of the manifestations of malignant disease, has become a well recognized phenomenon during recent years. In 1953 Woodard [1] reported that about nine per cent of patients with metastases to bones from primary sites other than the prostate showed elevations of total serum calcium. Myers [2, 3] has found high serum calcium levels frequently associated with carcinoma of the lung, breast, and kidney, in addition to multiple myeloma and the lymphomas. Other tumors that have been associated with hypercalcemia include malignant lesions of the stomach, cervix, urinary bladder, uterus, tonsils, cartilage, and neuroblastomas. As will be discussed later, the mechanism whereby this extremely serious, clinically troublesome, and sometimes fatal calcium excess comes about has never been clearly defined.[4] Indeed, it has been speculated as being unlikely that a single mechanism could explain all the cases described.[5] The purpose of this report is to describe a case of hypercalcemia associated with a metastasizing carcinoma of the cervix and to suggest a previously undescribed mechanism for the hypercalcemia associated with this malignant process. Consideration of this mechanism may aid the future clinical management of such cases.

CASE REPORT

A 34-year-old Negro mother of seven was admitted to the hospital on October 18, 1959, with chief complaints of left hip and leg pain and difficult bowel movements. One month following the uncomplicated birth of her last child in March, 1959, she began to have profuse vaginal bleeding. Pelvic examination in another hospital revealed a cervical mass, and subsequent biopsy showed an invasive grade 3 epidermoid carcinoma of the cervix. She was given an unknown amount of internal radium therapy as well as external x-radiation in April, 1959. Since that time there had been a 20 pound weight loss and during the two months prior to admission she had noted frequent episodes of chills and fever, dizzy spells, severe left hip and leg pain, and marked constipation. Past history was unremarkable and no significant familial diseases were noted.

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Admission physical examination revealed a blood pressure of 108/76 mm. Hg, temperature, 39.5° C, pulse, 114, and respirations, 20. She was a thin, malnourished-appearing female who could lie still without discomfort but who evidenced great pain on manipulation of the left hip and leg. A 1 by 2 cm. node was felt in the left inguinal region and a slightly smaller one in the right. The left pupil was larger than the right. No masses were palpable in the neck. Examination of the breasts, heart, and lungs was negative. Abdominal examination revealed no palpable organs, but

TABLE 1

Laboratory Findings

Date	Serum Calcium (mg. %)	Serum Phosphorus (mg. %)	Serum Alkaline Phosphatase (B.U.)	Urine Calcium (mg./day)	Therapy*
10/9/59	13.7	2.7	11.4		
10/26/59	19.8		12.4		
10/27/59 (1)	22.5	2.9			500 mg. Solu-Cortef
10/27/59 (2)	20.0				
10/28/59	17.5	3.8		805	200 mg. i.m.
10/29/59	17.4	3.5	10.0	470	200 mg. i.m.
10/30/59	16.5	3.4	8.4	550	200 mg. i.m.
11/2/59	16.9	3.9	9.8	269	200 mg. i.m.
11/5/59	12.1	3.1			200 mg. i.m.
11/9/59	13.3	4.3	10.6		200 mg. i.m.
11/12/59	11.1	3.4	12.4		100 mg. i.m.
11/17/59	11.8	3.3	18.0		25 mg. b.i.d.
11/23/59	13.6	3.6	16.5		25 mg. q.i.d.
11/25/59	14.1	3.4	14.4		25 mg. b.i.d.
11/28/59	19.3	3.2	12.5		50 mg. b.i.d.
12/1/59	19.0	3.6		307	500 mg. Solu-Cortef
12/2/59	20.0	2.8	8.4	409	400 mg. Solu-Cortef
12/3/59	17.3	2.8		242	400 mg. i.m.
12/4/59	18.6	3.1	13.2	439	300 mg. i.m.
12/5/59	16.8	3.0	15.0		300 mg. i.m.
12/7/59	15.6	3.4	13.2	403	300 mg. i.m.
12/9/59	14.4	3.9			200 mg. i.m.
12/11/59	16.8	3.8	11.0		150 mg. i.m.
12/12/59	15.7				40 mg. Meticorten
12/14/59	16.3				200 mg. i.m.
12/16/59	15.6	4.5			400 mg. i.m.
12/19/59	16.7	4.6			200 mg. i.m.
12/22/59	14.3				200 mg. i.m.
12/23/59	14.0				200 mg. i.m.
12/26/59		3.6			200 mg. i.m.
12/28/59	11.5	4.1			200 mg. i.m.
12/29/59	10.4				150 mg. i.m.
12/30/59	9.8	4.3			150 mg. i.m.
1/2/60	8.4	4.9			75 mg. i.m.
1/3/60	died				

* Therapy is cortisone acetate p.o. unless otherwise noted.

a 2 by 3 cm. firm mass was felt in the left lower quadrant adjacent to the pelvic brim. On pelvic examination the uterus was small and anteriorly placed, and the cervix was without visible lesions. Both the right and left adnexal areas were filled with firm, rigid, nodular masses of tissue extending to the pelvic walls. The patient refused to flex the left leg more than a few degrees, but no gross deformity was noted. Neurologic examination was not remarkable.

Admission laboratory findings included a hematocrit of 22.5%, white blood cell count of 20,500/cu. mm., and a urinalysis showing a specific gravity of 1.020, pH of

7.5, no sugar or protein, and 10 to 20 white blood cells per high power field. The findings pertaining to the calcium metabolism are listed in Table 1. Serum electrolytes (Na, K, Cl, CO_2) were normal throughout her course except for severe hyponatremia associated with the terminal episode. Blood urea nitrogen was within normal limits except for a transient rise to 49 mg.% in late December with a subsequent fall to 29 mg.% the day prior to death. Cephalin flocculation, thymol turbidity, transaminase, icterus index, cholesterol, and prothrombin time were consistently within normal limits. The total serum protein on numerous occasions varied from 6.4 to 8.1 gm.%, and the albumin fraction was constantly depressed below 3 gm.%. Skin tests with old tuberculin in dilutions as low as one in 1,000 were negative. Urine and blood cultures were all sterile on numerous occasions. An intravenous pyelogram showed a nonfunctioning left kidney and retrograde pyelography revealed obstruction to the left ureter by a pelvic mass. Two radio-

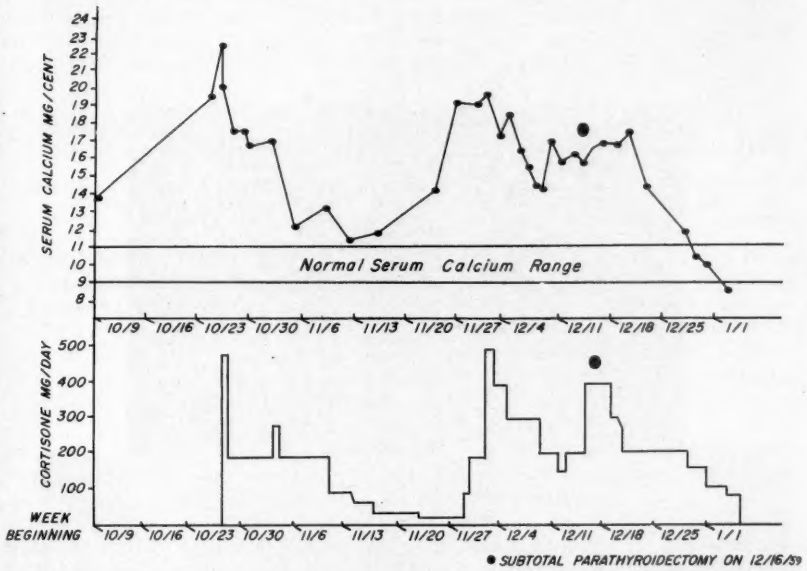

FIG. 1. Serum calcium values and cortisone dosage during hospitalization.

graphic surveys of the skeleton for metastases were negative. Biopsy of the enlarged left inguinal node showed only fibrosis, hemosiderosis, and slight reticuloendothelial hyperplasia. Hematologic workup revealed a bone marrow showing myeloid hyperactivity and erythroid hypoplasia suggesting a benign reactive response to inflammation. Hematocrit was maintained between 20 and 30% with a total of 4,300 ml. whole blood administered intermittently during the hospital course. It was felt that this patient was suffering from carcinoma of the cervix with extension and obstructive uropathy, secondary anemia and malnutrition, and probable nerve encroachment in the left pelvis as the cause of the leg pain.

On October 9, 1959 the serum calcium was noted to be 13.7 mg.%. Her sensorium was clear. On October 26 she was quite disoriented and a serum calcium of 19.8 mg.% was found. This rose to a high of 22.5 mg.% on the morning of October 27 when therapy was begun with 500 mg. intravenous hydrocortisone over

a 24-hour period. Subsequent therapy and data on calcium concentrations are recorded in Table 1 and are shown graphically in Figure 1. There was initially an excellent response to the steroids with a reduction of the serum calcium to 11.1 mg.% after two weeks of therapy, accompanied by marked sensorial improvement. However, with the reduction in cortisone dosage to less than 100 mg./24 hr., the calcium began to rise culminating in another symptomatic hypercalcemic crisis on December 2, 1959, with a serum level of 20 mg.%. Steroid therapy at that time, although more sustained and in higher doses than before, could not reduce the serum concentration below approximately 15.5 mg.%. Another skeletal survey now showed bony erosion of the left pelvis.

On December 16 simultaneous neck and pelvic explorations were done. Pelvic laparotomy revealed a blocked left ureter, and a biopsied abdominal node showed undifferentiated epidermoid carcinoma. The neck exploration revealed slightly enlarged parathyroid glands, three of which were removed. These glands weighed 0.1 gm. each and microscopic sections showed very sparse fat between the epithelial cells (Figure 2). No large "water clear" cells were seen, but the parenchymal cells generally had slightly more finely granular or vacuolated cytoplasm than the normal.

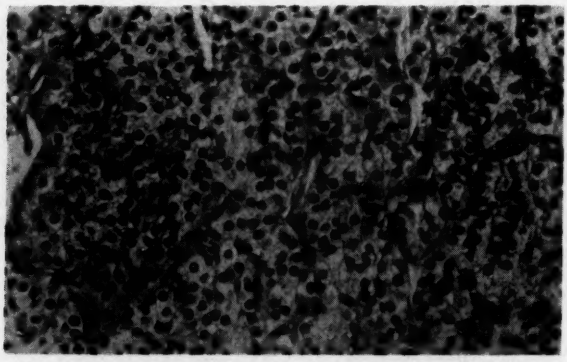

FIG. 2. Photomicrograph of a surgically excised parathyroid showing mild secondary hyperplasia (predominantly chief cell). × 300.

Some cells had an oxyphilic cytoplasm. The general histologic pattern tended to resemble the secondary hyperplasias [6] seen in some patients with severe renal failure. In the postoperative period cortisone therapy was maintained at preoperative levels. Six days after the operation the serum calcium began a striking and continuous decrease which persisted in almost a straight line fashion down to a low point of 8.4 mg.% on the day prior to death despite continuous reduction in steroid dosage (Figure 1). The patient died quietly on January 3, 1960.

At autopsy a large mass was found in the uterine cervix with metastases in the liver, lungs, and pelvic lymph nodes. Multiple abscesses of the left abdominal gutter and a neck abscess under the surgical scar were also present. Other findings included bilateral hydroureter, acute pyelonephritis, acute gastric ulcers, and acute bronchitis. Careful dissection of the entire neck area revealed the fourth parathyroid gland which was similar in histologic appearance to the previously removed specimens and likewise showed a secondary hyperplasia. Sections of bone from the left ilium showed considerable replacement by tumor and active osteoclastic resorption of the adjacent bone (Figure 3), but no tumor could be demonstrated in sections from other bones (vertebrae, ribs, and sternum). There was, however, evidence of recent osteo-

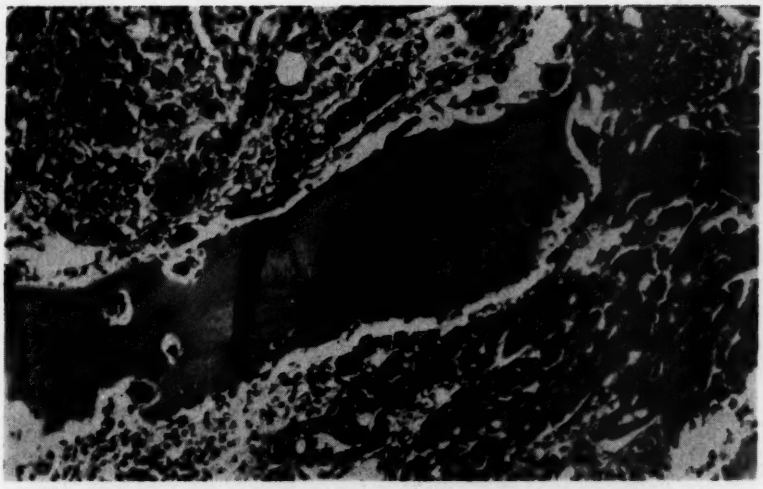

FIG. 3. Photomicrograph of undifferentiated epidermoid carcinoma in left ilium. Note numerous osteoclasts between the tumor and this bone spicule. × 300.

clastic resorption of these other bones. Haversian spaces in the cortex of a rib were enlarged and had scalloped margins representing the "toothmarks" of osteoclasts (Figure 4). Many trabeculae of cancellous vertebral bone also show evidence of recent osteoclastic destruction (Figure 5). No "dissecting osteitis" (which has been seen in some other cases of malignant disease and hypercalcemia [7] and which is a frequent histologic hallmark of hyperparathyroidism) was observed in the bone specimens available for study in this case. As expected from the massive cortisone

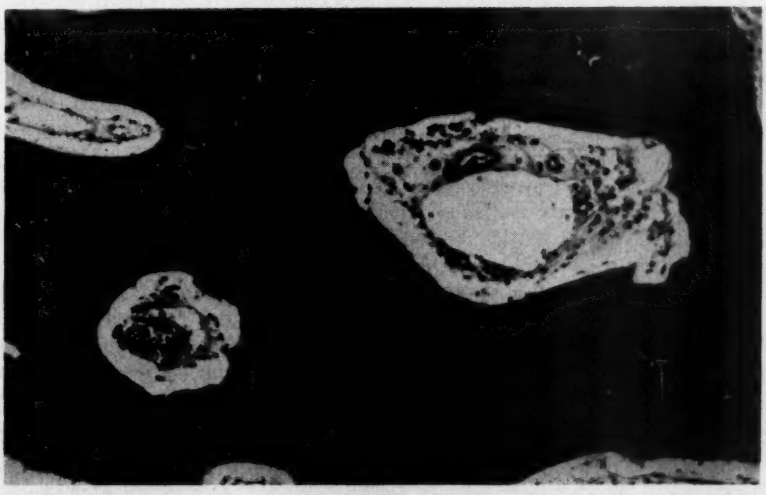

FIG. 4. Photomicrograph showing osteoclastic destruction of the cortex of a rib. × 120.

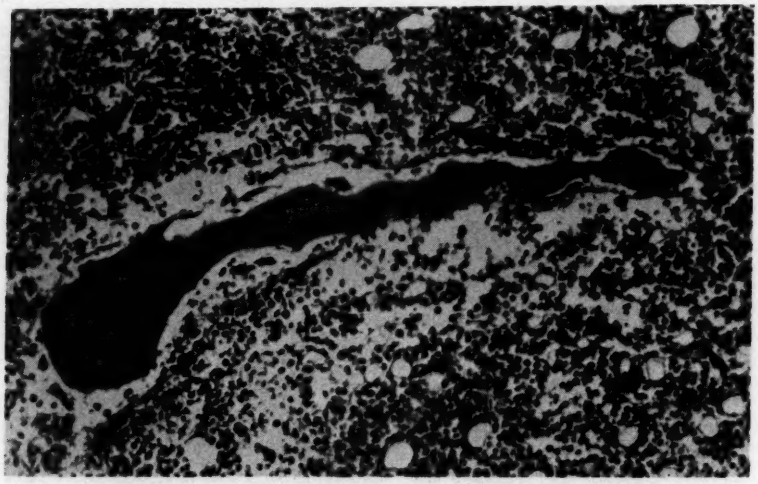

FIG. 5. Photomicrograph showing severe osteoclastic destruction of a vertebra. × 150.

therapy, both adrenals exhibited cortical atrophy. The osteoclastic resorption of bone described above is thought not to have been due to the corticosteroid treatment, because such marked cellular activity is not generally seen in patients with hypercorticism.[8]

DISCUSSION

Although this patient had known malignant disease, she still presented a problem in the differential diagnosis of hypercalcemia and its subsequent treatment. The numerous causes of hypercalcemia have been well documented in other reports.[2, 3, 9, 10] Only three possible causes were seriously considered in this case: sarcoidosis, primary hyperparathyroidism, and malignant disease. The clinical course, and more especially the autopsy findings, rule out sarcoidosis and primary hyperparathyroidism. It is therefore concluded that the diagnosis of hypercalcemia secondary to malignant disease is well established.

Three possibilities have been postulated as to the mechanism of the elevated serum calcium in association with malignant disease. The first hypothesis suggests that the hypercalcemia is secondary to the bone metastases with breakdown of the bone matrix and subsequent release of more calcium into the circulation than can be cleared by the kidneys (Figure 6, step 1). Studies in the past four years, however, have shown that this explanation is inadequate in many instances. Plimpton and Gellhorn,[11] as well as others,[12-15] described cases of hypercalcemia of malignant disease without evidence of bone destruction by tumor in the majority. Furthermore, removal of the primary tumor in some patients was followed by prompt reduction in the serum calcium level. They described no abnormalities in the parathyroid glands of nine of these cases. A second suggestion [11] is that the tumors might produce a substance like vitamin D causing increased calcium absorption from the gastrointestinal tract similar to the defect noted in Boeck's sarcoid.[16-19] The third theory is that the tumor produces a substance with properties like parathormone which is responsible for

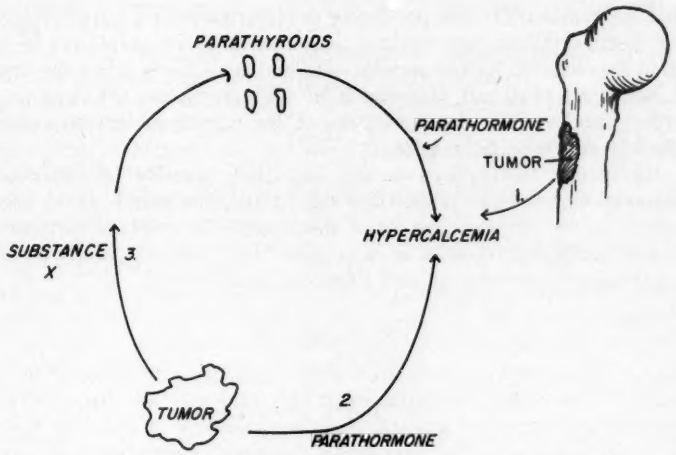

FIG. 6. Possible mechanisms of hypercalcemia of malignancy.

the hypercalcemia (Figure 6, step 2). Albright and Reifenstein [6] and Connor et al.,[14] as well as Plimpton and Gellhorn, have suggested this possibility. A case report in 1951 [20] possibly lends further credence to this hypothesis in describing parathyroid activity in a mediastinal tumor of unknown origin. The possibility that the mass may have been parathyroid tissue itself makes it difficult to draw any definite conclusions from the report.

The findings in the present case do not seem to be adequately explained by any of the above-mentioned theories. The hypercalcemia could not have been due to the autonomous breakdown of bony metastases pouring excess calcium into the circulation, for if this were so, the subtotal parathyroidectomy would not have produced the observed results in lowering the serum calcium. The possibility of increased gastrointestinal absorption of calcium has probably been ruled out by the normal fecal calcium excretion (Table 2). Third, it seems un-

TABLE 2

Calcium Balance as Calculated from a Controlled Intake-Output Study*

Date	Serum Calcium (mg. %)	Calcium Intake† (mg./day)	Urine Calcium‡ (mg./day)	Fecal Calcium§ (mg./day)	Calcium Balance (mg./day)
12/8	14.4	344	323	307	−286
12/9	14.4	344	323	307	−286
12/10	—	344	323	307	−286
12/11	16.8	344	323	307	−286
12/12	15.7	344	323	307	−286
12/13	—	344	323	307	−286

* Patient received an average of 200 mg. cortisone acetate per day or its equivalent during the six-day period.
† Measured diet analysis.
‡ Calculated daily average of measured urinary excretion of 1,939 mg. per six-day period.
§ Calculated daily average of measured fecal excretion of 1,843 mg. per six-day period.

likely that the tumor mass was producing parathormone or a parathormone-like substance, because if such were the case, intact parathyroids would not be needed to maintain the observed hypercalcemia. It thus seems likely that some unknown product, which we shall call "Substance X" (Figure 6, step 3), was produced by the tumor and resulted in stimulation of the parathyroids with consequent hypercalcemia and bone destruction.

The therapeutic implications of this case may possibly be important. If other observations confirm the fact that the parathyroid glands are a necessary intermediate in the development of a disturbance in calcium metabolism in patients with malignant disease, it is possible that subtotal parathyroidectomy may be warranted in certain selected situations of this type.

Summary

A case of hypercalcemia associated with metastatic carcinoma of the cervix is presented. The reasons for arriving at this diagnosis are discussed and the striking therapeutic effect of subtotal parathyroidectomy in reducing the serum calcium is documented. The previously described mechanisms of causation of hypercalcemia associated with malignant disease are discussed, and a new pathway mediated through the parathyroid glands is postulated.

Summario in Interlingua

Es presentate un caso de hypercalciemia associate con carcinoma metastatic del cervice. Le mechanismo per le qual iste extrememente serie, clinicamente disturbante, e a vices mortal excesso de calcium es producite ha nunquam essite definite clarmente. Le presente communication suggere un previemente non describite mechanismo pro le hypercalciemia associate con iste processo maligne. Le frappante effecto therapeutic de parathyroidectomia subtotal in le reduction del calcium del sero es documentate. Le consideration de iste mechanismo va possibilemente adjutar le futur tractamento clinic de tal casos.

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HYPERPARATHYROIDISM ASSOCIATED WITH PAGET'S DISEASE*

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THE clinical, biochemical, radiologic, and histopathologic findings of hyperparathyroidism are sufficiently characteristic in the majority of instances to allow the diagnosis to be made with a fair degree of certainty prior to surgical exploration. Occasionally, however, difficulty is encountered. Atypical features may be present which render the preoperative diagnosis uncertain. When another disorder coexists, which, in itself may present features similar to those seen in hyperparathyroidism, making the diagnosis is apt to be especially difficult.

In the present case the patient was found to have typical radiologic evidence of Paget's disease, confirmed by bone biopsy. Certain features, however, were atypical and led to more detailed studies. Coexistent hyperparathyroidism

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was then suspected and subsequently confirmed by the finding of a parathyroid adenoma on exploration of the neck.

Case Report

A 52-year-old white man was admitted to the Veterans Administration Hospital, Philadelphia, Pennsylvania on March 9, 1960, with a chief complaint of pain in the low back and right hip. Three days prior to admission he had slipped on ice and landed on his buttocks. Following this he experienced severe pain in the right hip and low back, rendering ambulation impossible. Roentgenograms taken at another hospital revealed a fracture of the superior ramus of the right pubic bone and areas of osteoblastic proliferation throughout the pelvis.

The past medical history was essentially negative except for surgical incision and drainage of the left lateral region of the neck in childhood for swollen glands. On systemic review, he denied any symptomatology prior to the fall. The patient's wife, however, stated that he had experienced increasing polyuria and polydypsia for a two-year period and intractable constipation for one year prior to admission. The insidious onset of generalized muscle weakness had been present for six months.

Physical examination on admission revealed a somewhat obese white man complaining of pain in the right hip and lumbar spine. The temperature was 99.6° F., pulse 100 per minute, blood pressure, 120/80 mm. Hg. There was a well healed surgical scar in the left lateral neck region. No masses were palpable in the neck. The corneas were free of opacification and haziness. There was no enlargement or deformity of the skull. The teeth appeared to be in excellent condition. Examination of the ears, nose, throat, heart, lungs, abdomen, and rectum was within normal limits. Examination of the musculoskeletal system revealed a normally proportioned though slightly obese configuration. There was marked tenderness just to the right of the symphysis pubis, but no other abnormalities were noted.

The following laboratory studies were within normal limits: hemoglobin, hematocrit, white blood cell count and differential, total protein and albumin-globulin ratio, acid phosphatase, serologic test for syphilis, blood urea nitrogen, blood sugar, and creatinine. Urinalyses showed from 20 to 30 white blood cells per high power field but were otherwise normal. Two urine cultures were sterile and examination of the urine for Bence Jones protein was negative.

The values for serum calcium ranged between 12.2 and 13.7 mg./100 ml. on numerous occasions. The serum phosphorus ranged between 1.9 and 3.5 mg./100 ml. with eight of 11 determinations being below 2.5 mg. The alkaline phosphatase varied from 8.8 to 22.7 Shinowara units with all but one of seven determinations being over 10 units. Two 24-hour urine specimens collected after a standard three-day low calcium diet contained 140 and 60 mg. of calcium. An electrocardiogram was within normal limits. Chest roentgenogram revealed no abnormality of the heart or lungs. A complete roentgenographic skeletal survey was performed. Slight demineralization was present in all bones and particularly in those of the skull and the hands. There was no subperiosteal bone resorption. The left femur and first left metacarpal bones had areas of radiolucency surrounded by sclerotic foci. Roentgenograms of the pelvis revealed moderate demineralization, with areas of patchy radiolucency surrounding linear areas of marked sclerosis (Figure 1). A recent fracture was present in the superior ramus of the right pubic bone. The entire radiologic picture was felt to be strongly suggestive of Paget's disease of bone, but associated hyperparathyroidism was an additional consideration. An intravenous urogram was within normal limits. Neither calculi nor nephrocalcinosis were present. The lamina dura of the teeth was intact and normal bone surrounded the teeth.

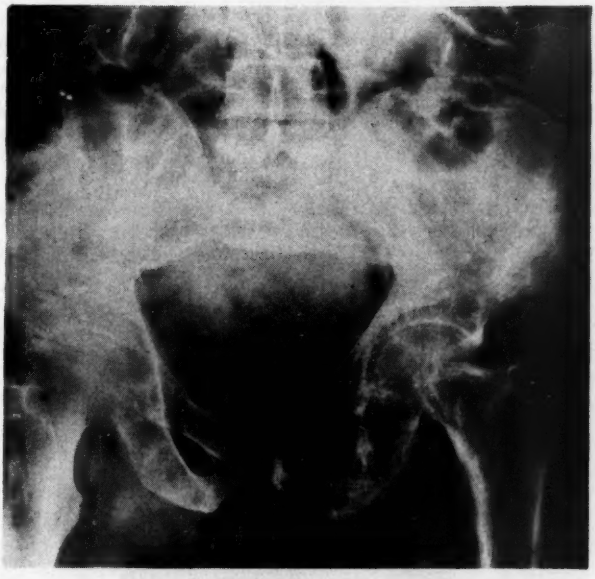

FIG. 1. Roentgenogram of the pelvis showing demineralization changes suggestive of Paget's disease, and fracture of the superior ramus of the right pubic bone.

Following admission to the hospital, the patient was placed at bed rest and given symptomatic therapy for the pain of the pubic fracture. On the fifteenth hospital day, a bone biopsy was obtained from the left iliac crest. Microscopically the bone spicules showed irregular widening with marked disorganization and irregularity of the cement lines (Figure 2). Moderate osteoclastic activity was present. Osteo-

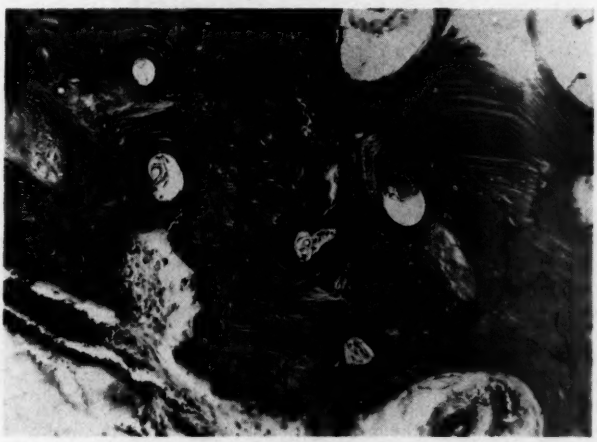

FIG. 2. Photomicrograph of biopsy of ilium showing thickened trabeculae of bone with prominent cement lines. H. & E. × 90.

blastic activity was also evident. The marrow contained loose fibrous tissue and was hypervascular. The microscopic picture was felt to be characteristic of Paget's disease.

Despite the obvious presence of moderately advanced Paget's disease as demonstrated radiologically and by microscopic examination, this disease was thought inadequate to explain the persistent abnormalities of calcium and phosphorus levels, since hypercalcemia persisted even after the patient had been ambulatory for several days. Accordingly, a four-hour renal phosphorus reabsorption test was performed.[1] With a urine flow of 730 ml. during the test period, the per cent of tubular reabsorption of phosphorus was 67.4, with a phosphorus clearance of 75 ml. per minute.[2] This test was repeated one week later, and with a flow of 1,300 ml. during

FIG. 3. Roentgenogram of barium-filled esophagus showing deviation by cervical mass.

the test period there was a phosphorus reabsorption of 61% and the phosphorus clearance was 52 ml. per minute. All of these values represented substantial abnormalities, and, in the absence of any evidence of renal disease, were felt to be strongly suggestive of hyperparathyroidism. In addition, a cortisone suppression test performed over a 10-day period did not significantly alter the sustained hypercalcemia.[3] This finding also was felt to be compatible with hyperparathyroidism.

A radiologic study of the upper esophagus revealed a smooth, rounded defect approximately 3 cm. in diameter impinging upon the esophagus from the left side at the level of the thoracic inlet (Figure 3).

Surgical exploration of the neck region was performed on May 11, 1960. A tumor measuring approximately 3 by 2 by 1 cm. was removed from the region of the left inferior parathyroid gland (Figure 4). Microscopic examination revealed

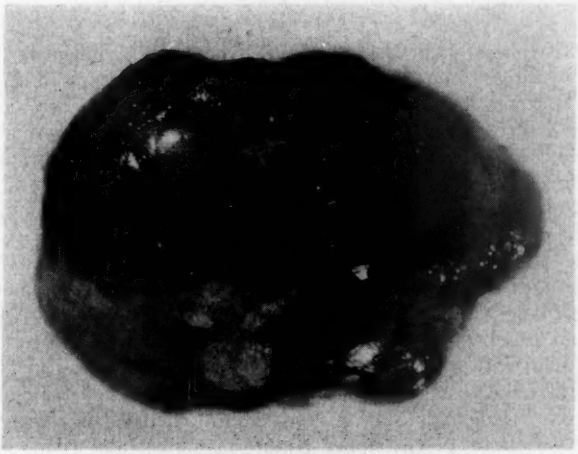

FIG. 4. Adenoma measuring 3 by 2 by 1 cm. removed from region of the inferior parathyroid.

a highly cellular chief cell adenoma (Figure 5). The remaining three parathyroid glands were grossly normal.

The patient made an uneventful recovery. No overt or latent signs of hypocalcemia were noted. There was a prompt subsidence of polydypsia, polyuria, and constipation, and muscle strength was subjectively increased. The serum calcium level returned to normal on the third postoperative day and remained normal throughout the remainder of the hospital course. A phosphorus reabsorption test on the seventh postoperative day was 90% and the phosphorus clearance was 11.9 ml./min. The patient was discharged, asymptomatic, on his eightieth hospital day.

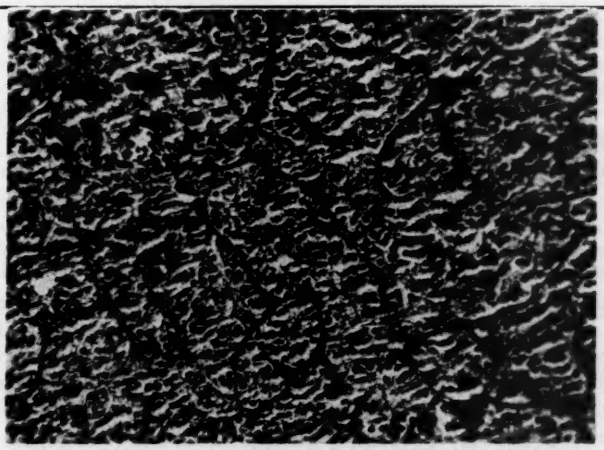

FIG. 5. Photomicrograph of parathyroid adenoma showing fairly uniform trabecular arrangement of chief cells and occasional acinar forms. H. & E. × 180.

Discussion

The coexistence of Paget's disease and hyperparathyroidism has been noted previously. Albright and Reifenstein [4a] mention four cases of hyperparathyroidism complicated by Paget's disease, but case reports are not provided. Zimmerman described a 39-year-old woman with diffuse abnormalities of the pelvic bones, the long bones, and the phalanges on roentgenographic studies.[5] Changes were present in the skull which were felt to be typical of Paget's disease. Hypercalcemia and hypophosphatemia led to an exploration of the neck and the finding of an adenoma of a parathyroid gland. Five years after surgery, the patient was re-evaluated radiologically and was found to have advanced changes in the bones of the chest, pelvis, skull, femur, and phalanges which were thought to be typical of Paget's disease. However, no histologic proof of the presence of Paget's disease was provided. Rosen [6] reported a 43-year-old man with a long history of pain in the extremities and renal lithiasis. Polyuria, polydypsia, constipation, and nausea were reflective of underlying hypercalcemia. Radiologic survey revealed the changes of Paget's disease in the lumbar vertebrae, pelvis, upper femur, mandible, and ribs. At the same time, there were lytic areas in the ilium and femur suggestive of the "brown tumors" of hyperparathyroidism. The lamina dura was absent. Biopsy of the left ilium showed a typical "brown tumor" of hyperparathyroidism. In addition, biopsy of the femoral subtrochanteric area revealed changes both of Paget's disease and hyperparathyroidism. An epulis tumor was found in the mouth which was typical of the "giant cell epulis tumor" of hyperparathyroidism. At surgical exploration of the neck, a left inferior chief cell parathyroid adenoma was found.

Other examples of the coexistence of these two diseases have been noted.[7-9] In addition, cases are described which had been followed for years with the presumptive diagnosis of Paget's disease only to find at autopsy or upon careful clinical and biochemical reappraisal [10] that the entire picture was explained by a parathyroid adenoma.

The present case differs from those previously described in that the diagnosis of hyperparathyroidism was confirmed ante-mortem in a relatively asymptomatic patient with histologically proved coexistent Paget's disease and with a biochemically demonstrable abnormality of renal phosphorus clearance, which was corrected by removal of the parathyroid adenoma. In addition, the absence of hypercalciuria and renal lithiasis and the persistence of the lamina dura tended to obscure the diagnosis of hyperparathyroidism.

When seen alone with its characteristic manifestations neither hyperparathyroidism nor Paget's disease usually constitutes a difficult diagnostic problem. Occasionally, however, certain features of one may simulate the other and lead to a difficult differential problem. Both diseases are capable of causing deformity of the skeletal system; bone pain is a symptom in common; the alkaline phosphatase may be elevated in both; and increased marrow fibrosis and vascularity are common histologic features of both diseases.[11a] Renal lithiasis, hypercalcemia, and hypercalciuria occasionally occur in Paget's disease and are common findings in hyperparathyroidism.[4b, 12, 13]

In advanced cases of hyperparathyroidism the radiologic features of Paget's disease have been noted to develop years after parathyroidectomy.[5, 11b, 12] The

assumed identity of the two disorders in the past has led to the performance of parathyroidectomy in some cases of Paget's disease.[4a, 14] On the other hand, parathormone has been administered to patients with Paget's disease with some reported relief of bone pain.[15] Albright believes it possible that the presence of hyperparathyroidism may predispose to the development of Paget's disease and it has been his practice to rule out hyperparathyroidism in all cases of Paget's disease.[4a] In his series of cases, however, this procedure failed to uncover any cases of hyperparathyroidism.

It appears to be well established that the two disorders have basically different identities. Autopsy studies in patients with Paget's disease have failed to uncover any consistent abnormality of the parathyroid glands.[6] The basic clinical and biochemical distinctions between the two diseases have been repeatedly emphasized since Schmorl's detailed description in 1932.[16] The increased use of roentgenography and the refinement of tests of parathyroid function make possible the diagnoses of Paget's disease and hyperparathyroidism long before their classical findings are apparent. Three per cent of individuals above the age of 40 are said to manifest some degree of Paget's disease.[4a] In view of this high incidence, the occurrence of a parathyroid adenoma in an individual with Paget's disease may be regarded as a coincidence.

Summary

A case of hyperparathyroidism associated with Paget's disease is presented. There is no evidence that the two disorders are related, and their coexistence in the same individual must be regarded as a coincidence.

As exemplified by this case, however, the finding of Paget's disease should instigate a careful search for the presence of hyperparathyroidism, since the one may closely simulate the other and the two may even coexist.

Summario in Interlingua

Es reportate le caso de un masculo de 52 annos de etate con evidentia clinic e roentgenologic de hyperparathyroidismo in association con morbo de Paget. Es concludite que il existe nulle supporto pro le these que le duo disordines es relationate. Es opinate que le co-existentia del duo morbos in le mesme individuo debe esser reguardate como un coincidentia.

Tamen, como le presente caso lo illustra, le constatation de morbo de Paget deberea instigar un meticulose scrutinio pro le presentia de hyperparathyroidismo, viste que le un pote simular le altere multo illudentemente e viste etiam que le duo pote co-exister.

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CONCOMITANT HYPERPARATHYROIDISM AS A CAUSE OF THE HYPERCALCEMIA ASSOCIATED WITH HYPERTHYROIDISM *†

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The hypercalcemia reported as occurring in association with hyperthyroidism has been thought by some authors to be caused in some way by the thyrotoxicosis. It is the purpose of this paper to report a patient in whom the hypercalcemia associated with hyperthyroidism was caused by a concomitantly hyperfunctioning parathyroid adenoma. A review of other hypercalcemia cases reported with hyperthyroidism as possibly being caused by concomitant hyperparathyroidism has emphasized interesting possibilities regarding the effect of propylthiouracil on the serum calcium level in hyperparathyroidism.

Case Report

A 37-year-old woman, wife of a missionary, developed thyrotoxicosis in August, 1957, while living in the British West Indies. Her clinical illness was characterized

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by a lack of energy, loss of weight, emotional lability, increasing nervousness and irritability, and palpitation accompanied by breathlessness on exertion. These symptoms developed insidiously over a period of several months. Examination revealed an exhausted, afebrile, moderately anemic woman who had a fine tremor of the outstretched hands, a tachycardia with occasional extrasystoles, a slight, diffuse enlargement of the thyroid gland, and minimal thyrotoxic eye signs (prominence of the eyes, with a slight stare, lid retraction, and lid lag).

The only antithyroid drug immediately available in the patient's medical community was methylthiouracil; she was started on 50 mg. three times a day, and had a rapid and gratifying clinical response. The medication was reduced after 14 days to 50 mg. daily for an additional week. On a maintenance dose of 25 mg. every other day, a complete remission of her thyrotoxic condition occurred. In late December, 1957, there was a sudden appearance of ulceration of the mouth, and the methylthiouracil was promptly stopped. Leukocyte counts revealed a distinct neutropenia and a relative lymphocytosis. Serial counts obtained over a period of two to three weeks revealed a gradual return to a normal total and differential count, and no serious consequences developed from use of the thiouracil preparation.

The patient was first seen at the Caylor-Nickel Clinic on May 6, 1958, with an obvious exacerbation of thyrotoxicosis, characterized by nervousness, palpitation, weight loss, tremor, and breathlessness on exertion. Significant physical findings at this time were a tachycardia of 130, a blood pressure of 118/70 mm. Hg, mild exophthalmos with a slight lid lag, and a large, diffuse goiter with no definite nodules. A distinct, fine tremor was noted in the hands. In addition, the patient had some right flank tenderness, and her past history was significant in that she had experienced recurrent attacks of urinary urgency, burning, and frequency which had been previously treated as a coliform genitourinary infection. Thyroid function studies obtained shortly after hospitalization revealed a basal metabolic rate of plus 51%, a protein-bound iodine of 12.5 μg.%, and an I^{131} uptake of 59% in 24 hours. Following these studies, an intravenous pyelogram revealed a large right staghorn calculus. The patient was found to have an elevated serum calcium (12 to 13.3 mg.%), with a serum phosphorus of 3.1 to 4.2 mg.%, and a low tubular phosphorus reabsorption of 10 to 20%. During this hospitalization a lumbar puncture was performed specifically to obtain a spinal fluid calcium level, which was 5.3 mg.% when the serum calcium averaged 13 mg.%

After 23 days' preparation with Lugol's solution, the patient sustained a successful subtotal thyroidectomy. A careful, though unsuccessful, search for a possible associated parathyroid adenoma was undertaken. These efforts were somewhat limited by excessive bleeding during the procedure, as the gland was quite friable and vascular. The patient improved following the thyroidectomy, and was discharged from the hospital on June 7, 1958, in a euthyroid condition, although her serum calcium remained elevated.

On September 26, 1958, a large staghorn calculus (calcium phosphate stone) was removed from the right kidney pelvis. The patient made an uneventful postoperative recovery following a rather severe febrile episode, and was discharged on October 11, 1958.

In view of the persistent hypercalcemia and the danger of subsequent nephrolithiasis, the patient was placed on a low calcium diet. The calcium excretion studies undertaken proved to be within normal limits (172 mg. in 24 hours). To rule out an occult sarcoidosis as the etiologic factor in her hypercalcemia, cortisone was tried empirically for a period of three weeks, but no significant change was noted in serum calcium levels. At this time, surgical re-exploration of her neck was considered to determine whether the presence of a parathyroid adenoma was causing her evident hyperparathyroidism. An ultrafiltrable calcium, elevated to 7.9 mg.% (total,

14 mg.%), helped to support the diagnosis of hyperparathyroidism. On January 11, 1959, the patient was admitted to the Clinic hospital for the fourth time, and on January 23, 1959, underwent a neck exploration. A nodule was found behind the left superior pole of the remaining thyroid gland, and it was proved pathologically to be a parathyroid adenoma. Remnants of thyroid tissue from the previous surgery were also excised. Subsequent serum calcium determinations (January 24, January 28, and January 30, 1959) were all within normal limits, ranging from 9.2 to 9.9 mg.%, with a serum phosphorus of 2.9 mg.% and a tubular phosphorus reabsorption of 84%. The patient was discharged on January 31, 1959, and when last examined, July 2, 1959, she was euthyroid, with a serum calcium of 10.5 mg.% and a serum phosphorus of 3.1 mg.%. Serum calciums have been determined on her mother and six of her 11 full siblings, without abnormalities being found.

Discussion

This case has suggested that the hypercalcemia found in some of the other reported cases of hyperthyroidism might also be explained by concomitant hyperparathyroidism. The association of hyperparathyroidism with hyperthyroidism has been verified pathologically as being caused by a parathyroid adenoma by Ballin and Morse,[1] Hellström,[2] Noble and Borg,[3] Miller and Evans,[4] and Aarseth and Bjorgo.[5] Hellström,[6] in 1954, felt that coexistent hyperfunction of the thyroid and parathyroid glands was not likely to be due to coincidence because of the number of these cases reported. Also discussed by Hellström [6] was the possibility that hyperfunction of the thyroid gland could in some way exert a stimulating effect on the parathyroid glands, and the reverse possibility, that hyperparathyroidism could stimulate the thyroid gland. Hellström felt that it was likely that the hypophysis which controls the thyroid gland might, either directly or indirectly, play some part in the changes in the parathyroid glands. We feel that the best explanation for the simultaneous hyperfunction of thyroid and parathyroid glands might lie in the concurrence of thyroid and parathyroid adenomas as a part of the syndrome of multiple endocrine adenomas, described by Underdahl et al.,[7] Wermer,[8] and Moldawer et al.[9]

Hypercalcemia has been observed in several cases of hyperthyroidism since the first report by Wijnbladh [10] in 1937. Puppel et al.[11] observed a transient hypercalcemia in three of six patients reported with hyperthyroidism. Huth et al.[12] observed a transient serum calcium elevation initially in a case of hyperthyroidism, and Green and Lyall [13] observed a high-normal serum calcium (11.5 mg.%) in one of six cases of hyperthyroidism reported. Hellström [6] assumed that hyperparathyroidism existed in one case of hyperthyroidism with hypercalcemia whose calcium returned to normal after a subtotal thyroidectomy. In this case no systematic examination had been made for possible parathyroid tissue within the thyroid gland that was removed. Other cases of hypercalcemia with hyperthyroidism have been reported by Stanley and Fazekas [14] (one case); Rose and Boles [15] (three cases); Pribek and Meade [16] (one case); and Epstein et al.[17] (one case). The data from these last eight cases are of particular importance. If one assumes that hyperparathyroidism existed in these cases, as it did in the case reported in this paper and in the other cases mentioned above, interesting possibilities can be considered regarding the modification of serum calcium levels by the use of propylthiouracil in hyperparathyroidism.

In the case reported by Stanley and Fazekas,[14] for instance, the serum cal-

cium was observed to fall from 13.1 to 10.3 mg.% after 36 days on 300 mg. of propylthiouracil a day. The serum calcium remained normal while the patient was on this therapy for one year, and was normal five months after discontinuation of therapy. This response to propylthiouracil was presented as evidence that the hypercalcemia was caused by the hyperthyroidism, but it could also be used as evidence that propylthiouracil may have lowered the serum calcium of an underlying, unrecognized hyperparathyroid state.

In case 1 of Rose and Boles [15] the serum calcium remained elevated for at least 12 days after thyroid surgery, dropping to 11 mg.% on the eighteenth day. We are unable to explain the serum calcium changes in this case by the concomitant presence of a parathyroid adenoma. There is, of course, the possibility that some local circulatory disturbances resulting from the operation might have decreased the function of a parathyroid adenoma which was present but undiscovered at the time of surgery.

The data on the second case reported by Rose and Boles [15] are not sufficient to state what effect propylthiouracil had on the serum calcium level, since only the range of variation (11.2 to 19.2 mg.%) during the period of drug administration is reported.

The serum calcium level in their third case [15] decreased from 14.1 to 16.9 mg.% down to 10.6 mg.% after two months on propylthiouracil, although it was still 13.2 mg.% after the first month on this agent.

In Pribek and Meade's case [16] the serum calcium decreased from 14.1 mg.% to 10.7 mg.% after six weeks on 400 mg. of propylthiouracil a day, even though the hyperthyroidism persisted. The patient required 5 mc. of I^{131} on two occasions to control the hyperthyroidism, even though the serum calcium remained normal after a total of 10 weeks of propylthiouracil.

The case reported by Epstein et al.[17] showed a fall in serum calcium from 15.8 mg.% to 10.9 mg.% after three months on 300 mg. of propylthiouracil each day, although the calcium was 14.2 mg.% after two months of treatment. This patient had 4.17 mc. of I^{131} at the onset of the propylthiouracil treatment. It is conceivable that this therapeutic dose of I^{131} may in some way have affected the function of a parathyroid adenoma. This may seem unlikely, but it could be possible if a parathyroid adenoma were buried within thyroid tissue. Temporary hypoparathyroidism following radioactive iodine treatment for thyrotoxicosis was reported by Tighe [18] in 1952. Freedberg et al.,[19] however, found pathologic abnormalities in the parathyroid glands of only one of nine euthyroid patients receiving 17 to 157 mc. of I^{131}.

In Sallin's case [20] the serum calcium decreased from 13 to 14 mg.% to 9 to 11 mg.% in one month on iodine and propylthiouracil therapy. The case reported by Kleeman et al.[21] showed a marked lowering of serum calcium on the high phosphorus diet, but also showed a decrease during treatment with propylthiouracil. Their case, cases 1 and 2 of Rose and Boles,[15] and the case reported by Pribek and Meade,[16] were normocalcemic even at the time of recurrent thyrotoxicosis. Kleeman et al.[21] felt that the excessive urinary and fecal calcium excretion in their case of thyrotoxicosis was due to the direct effect of thyroid hormone on osseous metabolism. They stated that the hypercalcemia was probably secondary to some disorder in homeostatic mechanism(s) regulating the content of ionized calcium in the extracellular fluid.

Laake,[22] in 1955, in reporting a case of hyperthyroidism with osteoporosis and multiple fractures, assumed hyperfunction of the parathyroid glands to exist despite a normal serum calcium. He felt that the simultaneous hyperfunction of both glands returned to normal under Tapazole treatment.

It seems possible that some of these cases might have had concomitant hyperparathyroidism. If this is true, then the experience in these cases might provide some rationale for investigating the effect of propylthiouracil on hyperfunctioning parathyroid tissue, since the serum calcium was lowered in five of eight of the above-mentioned cases while on this therapy. We are exploring this possibility by the use of propylthiouracil in three patients with hereditary hyperparathyroidism. These preliminary studies [23] have demonstrated a lowering of serum calcium levels in each of these patients on 300 to 450 mg. daily doses of propylthiouracil followed for five to six months. Although the mechanism of action of propylthiouracil in these cases is not understood, the present results suggest that further investigation of these findings might be important.

Summary

This paper reports the case of a 37-year-old woman whose serum calcium elevation to 13 mg.% was thought to be caused by her hyperthyroid state. Control of the thyrotoxicosis by subtotal thyroidectomy did not lower the serum calcium, which returned to normal only after excision of a parathyroid adenoma. The coexistence of thyroid and parathyroid adenomas in this case and others in the literature is thought to be more than coincidental. It is suggested that this concomitance might occur as a part of the syndrome of multiple endocrine adenomas. These cases suggest that the hypercalcemia found in some of the eight other reported cases of hyperthyroidism may be explained by concomitant hyperparathyroidism. A review of such cases from the literature revealed that a lowering of the serum calcium occurred with propylthiouracil therapy in five cases. If parathyroid hyperfunction coexisted in those cases, as it did in ours, then propylthiouracil may in some way be effective in lowering the serum calcium in hyperparathyroidism.

Addendum

Since submission of this manuscript, another report of a functioning parathyroid adenoma in a case of hyperthyroidism has appeared.[24] This paper mentions other reports of the concurrence of the two diseases. It is interesting to note that there was no decrease in the serum calcium level during a five-week period on Tapazole therapy.

König and Gubler (Schweiz. Med. Wschr. **89**: 369, 1959) also reported two cases of hypercalcemia associated with hyperthyroidism, with a decrease in serum calcium associated with the administration of carbimazole in both cases.

Summario in Interlingua

Iste communication reporta le caso de un femina de 37 annos de etate in qui le elevation del calcium seral ad 13 mg per 100 ml esseva reguardate como causate per su stato hyperthyroidic. Le regulation del thyrotoxicosis per thyroidectomia subtotal non reduceva le calcium del sero, le qual retornava a nivellos normal solmente post

le excision de un adenoma parathyroide. Le numero del reportos de occurrentias simultanee de hyperthyroidismo e hyperparathyroidismo excede lo que pote esser reguardate como accidental. Un explication possibile del concomitantia del duo morbos es que illos occurre como parte del syndrome de multiple adenomas endocrin. Le presente caso suggereva que le hypercalciemia notate in certes del octo altere citate casos de hyperthyroidismo es possibilemente explicabile per un concomitante hyperparathyroidismo. Un revista de tal casos revelava que un reduction del nivellos seral de calcium occurreva in cinque post therapia con propylthiouracil. Si hyperfunction parathyroide co-existeva in ille casos (como illo co-existeva in le nostre), alora il es possibile que propylthiouracil ha un effecto in le reduction del nivellos seral de calcium in hyperparathyroidismo.

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PHEOCHROMOCYTOMA AND DIABETES MELLITUS: REPORT OF A CASE WITH TRANSIENT EXACERBATION OF DIABETIC RETINOPATHY FOLLOWING REMOVAL OF THE TUMOR*

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The association of diabetes mellitus with pheochromocytoma has been reported but is unusual.[1] The occurrence of diabetic retinopathy in association with pheochromocytoma is apparently rare.[2] It is the purpose of this report to describe a patient with diabetes mellitus believed to be secondary to a pheochromocytoma and with diabetic retinopathy which continued to progress despite the amelioration of other evidences of diabetes following removal of the tumor.

Case Report

A 51-year-old Negro laborer was admitted to the U. S. Naval Hospital, Philadelphia, for evaluation of glycosuria which had been found by his family physician during a routine yearly physical examination done on the day prior to admission. The patient denied any symptoms of polyphagia, polydypsia, polyuria, recent weight loss, palpitations, tremor, diarrhea, muscle weakness, or fatigue. Past medical history revealed that he had been in good health until three years prior to admission, when he was treated for "an overactive thyroid" because of unexplained weight loss (10 to 20 pounds) and increased sweating. Complete symptomatic relief was obtained at that time with oral medications, the exact nature of which was unknown. Yearly physical examinations since 1955 were reported as normal except for the presence of intermittent hypertension. Systemic review revealed a continued preference for cold weather and light-weight clothing during the three years prior to admission, and

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impotence of sudden onset in 1952. There had also been bilateral intermittent claudication (calf) on walking two blocks, with no apparent increase in severity during the two years prior to admission. The family history was noncontributory and was specifically negative for diabetes mellitus and hypertension.

Physical examination upon admission revealed a thin Negro male in no distress. Blood pressure, 170/106 mm. Hg in the left arm, 176/110 mm. Hg in the right arm, and 190/120 mm. Hg in the left leg; pulse, 76 per minute; respirations, 20 per minute; temperature, 98.8° F. Funduscopic examination revealed the arterioles and venules to be normal in appearance, with an A/V ratio of 2:3. Three small, hard, yellow-white exudates were seen in the superior nasal quadrant of the left eye, and several central capillary microaneurysms were also present in the left eye. There was no A-V nicking, spasm, hemorrhage, or papilledema. The thyroid gland was not palpable, and no bruit was heard over the base of the neck. The point of maximal impulse was in the fifth left intercostal space, 7 cm. from the midsternal line. The rhythm was normal sinus, and there was a soft blowing grade 1 systolic murmur, heard best over the aortic area and along the right sternal border. The chest was clear to percussion and auscultation. The liver, kidneys, and spleen were not palpable, and there were no palpable abdominal masses. The genitalia were normal. The skin and nails of the feet were atrophic. The dorsalis pedis and posterior tibial pulses were absent bilaterally, but normal femoral pulses and weak popliteal pulses were present. Warm, moist palms and a mild tremor of the outstretched fingers were noted. The remainder of the examination was within normal limits.

Laboratory studies, including complete blood count, serum electrolytes, phenolsulfonphthalein excretion test, blood urea nitrogen, and creatinine, were within normal limits. Glycosuria initially, and persistent albuminuria and hyaline casts, were noted on serial urinalyses. The Fishberg concentration test revealed a peak specific gravity of 1.024. The total serum cholesterol was 355 mg.%, with 273 mg.% esters. The initial electrocardiogram showed left ventricular hypertrophy and strain. X-ray examinations of the chest and skull were normal.

The fasting blood sugar on admission was 328 mg.%, with a two-hour postprandial blood sugar of 368 mg.%. Subsequent administration of 20 units of NPH insulin daily maintained the blood sugar between 126 and 152 mg.%. Occasional sporadic blood sugar values of from 182 to 187 mg.% were noted with concurrent elevations of blood pressure. A histamine-provocative test for pheochromocytoma was positive, with an immediate rise from 110/65 mm. Hg to 220/120 mm. Hg. The latter pressure responded immediately to intravenous Regitine (phentolamine), 5 mg., with an abrupt, sustained drop to 160/80 mm. Hg. A paradoxic rise in blood pressure was noted with the Sodium Amytal test. Numerous initial attempts to elicit a pressor response by abdominal palpation, sudden change in position, milking the flanks, etc., had been unsuccessful; however, on the tenth hospital day a tumor mass in the left upper quadrant was palpated, with a resultant pressor response to 280/120 mm. Hg from a previous resting blood pressure of 170/100 mm. Hg. There was little change in pulse (80 to 88 per minute) associated with the phenomenon, and there were no subjective complaints or other objective signs. A blood sugar drawn at this time (approximately two hours postprandial) was reported as 186 mg.%. During this episodic blood pressure rise the intravenous injection of 5 mg. of Regitine brought about a precipitous drop in blood pressure (to 90/60 mm. Hg), where it remained for approximately 20 minutes before returning to a constant level of 110/80 mm. Hg. Urine catecholamines (determined chemically) were reported as 159 μg. per 24 hours; (normal range for the Pepper Laboratories, Hospital of the University of Pennsylvania: from 10 to 100 μg./24 hrs.). Bio-assay for urinary catecholamines was also positive.

The uptake of radioactive iodine (I^{131}) in one hour was 4%, and in 24 hours was 9%. The protein-bound iodine was 5.1 μg.%; the basal metabolic rate was plus 50% and, on repeat determination, plus 55%.

An intravenous urogram and retrograde pyelogram (Figure 1) revealed some lateral displacement of the left ureter just below the pelvis of the kidney. Retroperitoneal pneumography (Figure 2), combined with a bilateral retrograde pyelogram, revealed an area of increased density superimposed upon the left psoas shadow, immediately to the left of the vertebral column, and extending from the lower border

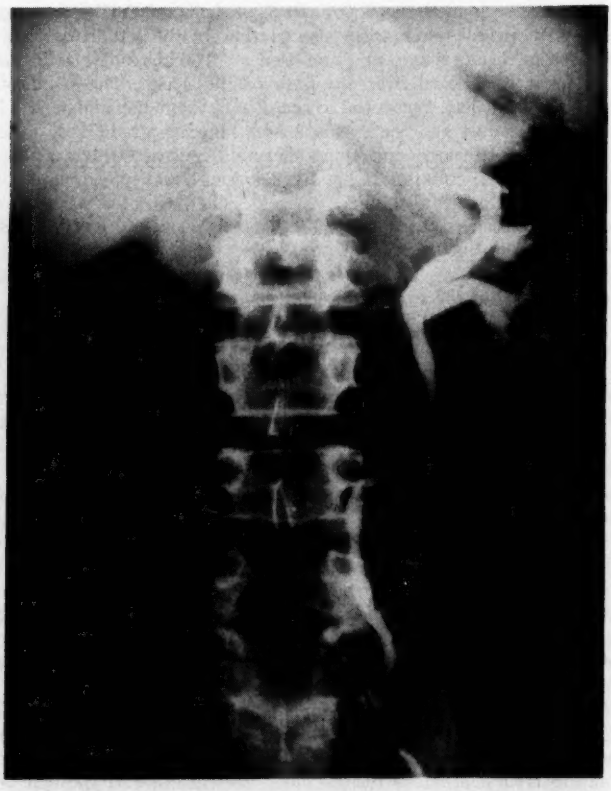

FIG. 1. Left retrograde pyelogram, demonstrating lateral displacement of the left ureter by the tumor mass.

of L2 to the upper border of L4. Multiple daily blood pressure determinations varied from 120/78 mm. Hg to 170/110 mm. Hg, and the pulse from 80 to 100 per minute. The only markedly hypertensive episodes elicited were those initiated by palpation of the tumor and by the histamine-provocative test.

On the twentieth day of hospitalization the patient underwent surgery. A left flank incision was made just under the twelfth rib, extending from the paraspinal muscles to the midline anteriorly. The retroperitoneal space was entered. Just inferior and medial to the kidney was a round, firm tumor. Gentle manipulation of

the tumor caused a marked rise in blood pressure. The tumor was freed by sharp and blunt dissection. One large vein and several smaller vessels were found and ligated. On removal of the tumor there was a sharp drop in blood pressure, necessitating the use of Levophed (levarterenol) intravenously. The left adrenal gland was normal to palpation. No other tumor was palpated along the aorta.

The resected tumor (Figure 3) consisted of an irregular globular mass, measuring 5.5 by 5 by 3.6 cm. and weighing 66.6 gm. It was encapsulated by firm, fibrous tissue, and was reddish-tan in color. The neoplasm was composed of soft brownish

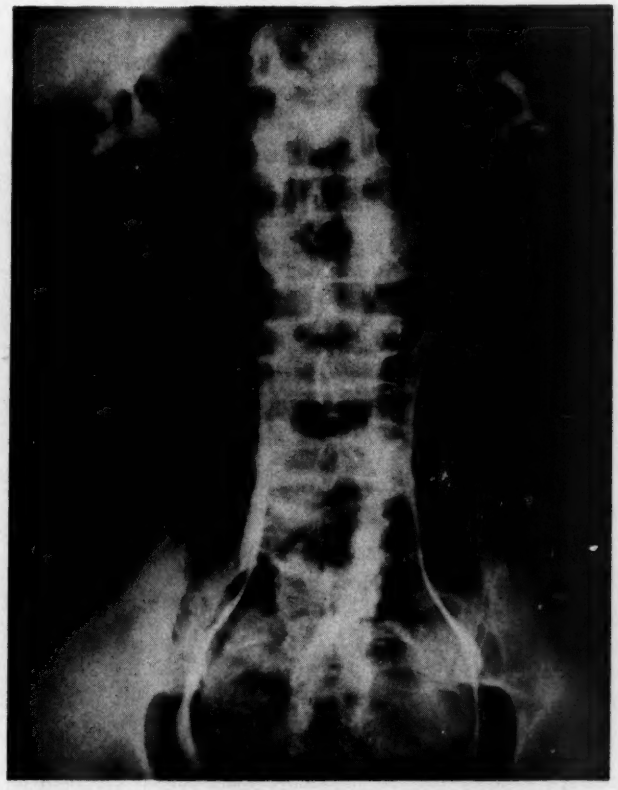

FIG. 2. Retroperitoneal pneumogram combined with bilateral retrograde pyelogram, outlining the tumor mass.

tissue, with focal areas of cyst formation containing brownish viscid fluid. A small, firm, fibrous central portion was present, with finger-like septa coursing through the mass. On microscopic examination (Figures 4 and 5) the tumor was composed of large polyhedral cells with large amounts of cytoplasm, moderate anisocytosis, and variable staining quality. Mitoses were infrequent. Some of the cells were multinucleated, and exhibited a horseshoe arrangement of the nuclei. The central portion of the tumor was made up of edematous hyalinized collagenous tissue with coarse septa. The pathologic diagnosis was pheochromocytoma (paraganglioma).

Postoperatively, pressor agents in the form of Levophed and subsequently Neosynephrine, intravenously, were necessary for a period of 24 hours. Throughout the remainder of hospitalization the blood pressure remained at approximately 120/70 mm. Hg. By the third postoperative day the patient was ambulatory and taking liquids by mouth. During routine physical examination five days postoperatively, marked funduscopic changes had been noted (Figure 6). One week prior to surgery only three small waxy exudates and a few scattered central capillary microaneurysms in the left fundus were seen; there were now noted in both fundi many large waxy and cotton-wool exudates, several flame-shape hemorrhages, and numerous central capillary microaneurysms. In the ensuing two weeks these changes became more pronounced, with further development of exudates and microaneurysms; however, in the following six weeks gradual regression of all of the previously noted fundic

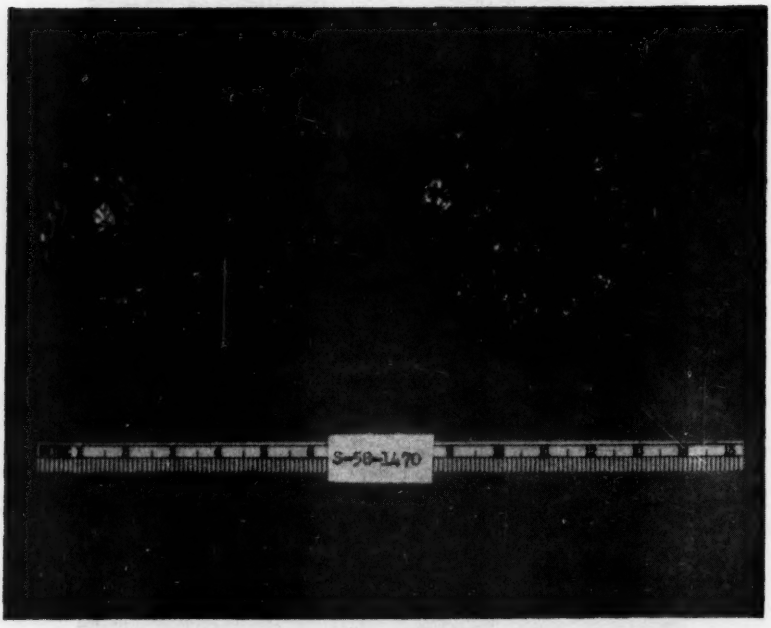

FIG. 3. Gross specimen.

changes occurred (Figure 7). At no time did the patient complain of any visual disturbance, or manifest any loss of visual acuity.

One week following surgery the patient complained of mild right calf pain, and was found to have a mild fever, moderate right pretibial and ankle edema, and a tender, hot, erythematous area over the medial aspect of the right calf. Homans' sign was not elicited. Slight edema was present over the left pretibial areas; there was no evidence of any inflammation. Treatment was begun for acute thrombophlebitis, consisting of bed rest, pressure dressings to the legs, local heat to the calves, and anticoagulation with heparin. The Lee-White coagulation time was maintained at approximately two and one-half to three times normal with 150 to 200 mg. of concentrated aqueous heparin given subcutaneously every 12 hours. Anticoagulant therapy was maintained for a period of 15 days, following which the patient gradually

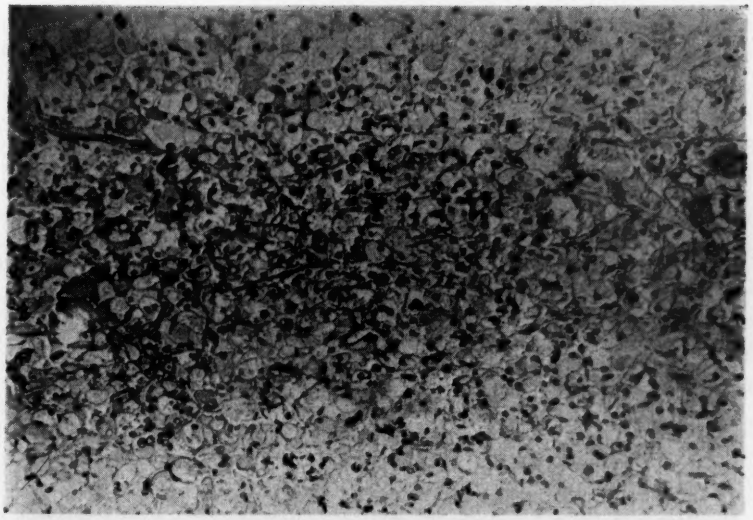

FIG. 4. Photomicrograph of the tumor, revealing large polyhedral cells. × 80.

became ambulant, using elastic stockings for support. There was no recurrence of the phlebitis or the edema.

The patient's last dose of insulin was on the day prior to surgery. Postoperatively he maintained normal fasting and two-hour postprandial blood sugars. On repeated examinations there was no further glycosuria. A glucose tolerance test

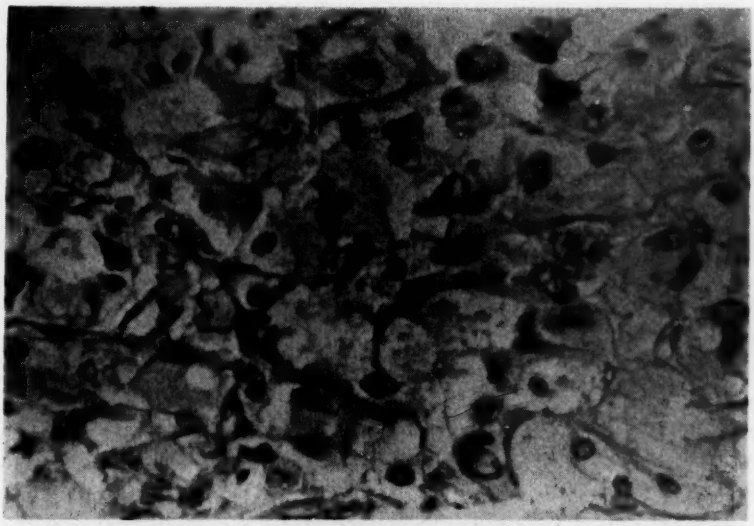

FIG. 5. Photomicrograph, demonstrating multinucleated cells. × 336.

FIG. 6. Left fundus, revealing the marked number of exudates and hemorrhage lateral to the optic disc. (Photograph taken one week postoperatively.)

revealed a fasting blood sugar of 105 mg.%, 114 mg.% at one-half hour, 153 mg.% at one hour, 132.5 mg.% at two hours, and 114 mg.% at three hours.

In further postoperative studies the histamine-provocative test gave a normal response, a 24-hour urine specimen for catecholamines revealed a value of 33 μg.,

FIG. 7. Photograph of left fundus, taken six weeks postoperatively, revealing marked regression of the previously noted lesions.

the bio-assay for catecholamines was negative, the protein-bound iodine was 3 μg.%, the basal metabolic rate was plus 10%, phenolsulfonphthalein excretion test was 30% in 15 minutes, a total eosinophil count was 87 per cubic millimeter, and the blood urea nitrogen, creatinine, serum electrolytes, complete blood count, platelet count, prothrombin time, bleeding time, and Lee-White coagulation time were all within normal limits. Pituitary gonadotropins were within normal limits. Postoperative urine and blood specimens for assay of adrenal cortical hormone levels were inadvertently misplaced. Radioactive vitamin B_{12} (cobalt-labeled) excretion was 10% in eight hours. (This test was performed during the period of resolution of the retinopathy.) The electrocardiogram revealed left ventricular hypertrophy without the previously noted strain pattern. The Rumpel-Leede tourniquet test was normal.

At the time of discharge from the hospital, six weeks postoperatively, the patient was asymptomatic, with a blood pressure of 130/84 mm. Hg. Examination of the optic fundi revealed some resolution of the previously described changes. Three months postoperatively, funduscopic examination revealed only several scattered waxy exudates and resolving hemorrhages in both fundi; no capillary microaneurysms were noted.

Discussion

In a review of pheochromocytomas in 1953, Levin [1] found that approximately 60% of the cases manifested fasting blood sugars greater than 120 mg.%, and that in 25 to 40% of these cases the glucose tolerance test was typically diabetic. It has been postulated that the hyperglycemia is due to sustained or episodic increases in the circulating catecholamines (noradrenalin and/or adrenalin) through their glycogenolytic action on liver and muscle glycogen.[2, 3] Cori [4] has shown that the amount of epinephrine necessary to produce the alterations in carbohydrate metabolism found in patients with pheochromocytoma is considerably smaller than the amount necessary to produce pressor effects. Application of this has been made by deVries [2] to explain the existence of signs and symptoms of diabetes mellitus and hyperthyroidism in patients with pheochromocytoma who do not manifest continuous hypertension. This observation appears to be confirmed by the present case, where persistent hyperglycemia, requiring 20 units of NPH insulin daily, was noted despite prolonged normotensive periods.

Most of the manifestations of diabetes mellitus disappear following surgical removal of a pheochromocytoma.[5] The first reported case of such an occurrence postoperatively was described by Duncan [6] in 1944, when a cause-and-effect relationship between the presence of a chromaffin tumor and diabetes was definitely demonstrated ante-mortem. However, cases have been reported where diabetes mellitus has persisted postoperatively, the mechanism postulated being islet cell exhaustion and degeneration secondary to prolonged epinephrine-induced hyperglycemia. In the case under discussion there was a marked progression postoperatively of a previously noted diabetic retinopathy, despite the complete amelioration of clinical and laboratory evidences of diabetes.

Diabetic retinopathy has not to our knowledge been previously described in association with a pheochromocytoma. Furthermore, such degenerative changes as retinopathy, neuropathy, etc., are alleged not to occur in "secondary" diabetes mellitus. Hollenhortz,[8] in reviewing the ocular changes associated with pheochromocytomas in a series of 66 cases, makes no mention of diabetic retinopathy. Adler [9] describes diabetic retinopathy as consisting of the presence of capillary microaneurysms in the macular area in association with hard, white, or yellow

waxy or soapy exudates scattered throughout the eyegrounds. It is recognized that hypertensive retinal changes, consisting of waxy and cotton-wool exudates, flame-shaped hemorrhages, and arteriolar narrowing, can occur in the presence of diabetes mellitus and hypertension. However, the capillary microaneurysms of hypertensive origin are described as peripheral rather than central in location. The basic factor or factors responsible for the retinal changes in diabetes mellitus remain obscure. Their occurrence and severity have generally been related to the degree of control and duration of the diabetes.[7, 13, 15] The average time between the known onset of diabetes mellitus and the appearance of diabetic retinopathy has been estimated at from 13 to 15 years.[15] Numerous authors have suggested that the appearance of diabetic retinopathy is secondary to hormonal influences, rather than to the duration or control of the diabetes itself. The pituitary-adrenal cortical axis has been incriminated [11, 12] by the following observations: (1) worsening of diabetic retinopathy during periods of stress;[18, 22] (2) arrest of progressive diabetic retinopathy in some cases by adrenalectomy and hypophysectomy;[10, 19–21] (3) development by nondiabetics of retinal capillary microaneurysms during ACTH or cortisone therapy, with complete subsidence following termination of treatment;[10, 24] (4) excretion by diabetics with retinopathy of a significantly larger amount of glucocorticoids than by diabetics without retinopathy;[10, 11, 22, 23] (5) absence in diabetics without retinopathy of an eosinophil response to ACTH injection, indicating a relative adrenal hypofunction as compared to those with retinopathy;[23] (6) 24% heavier than normal weight adrenals with excessive lipoid vacuolation of the zona fasciculata in an autopsy series of diabetics with retinopathy and Kimmelstiel-Wilson disease, in contrast to those with uncomplicated diabetes.[18, 22] However, the rare occurrence of diabetic retinopathy in patients with acromegaly and Cushing's disease or syndrome who have associated diabetes mellitus [10, 17] has been noted.

Becker has suggested that adrenal cortical function, diabetes mellitus, and an abnormal vitamin B_{12} metabolism are responsible for the appearance of diabetic retinopathy through some as yet unknown mechanism. He and his coworkers have devised a radioactive vitamin B_{12} excretion test, and have noted that diabetics without retinopathy have a decreased excretion as compared to nondiabetics, whereas the diabetic with retinopathy exhibits an excessive excretion averaging twice that of the nondiabetic. Since this response is similar to that of the nondiabetic following cortisone therapy, it suggests that increased secretion of adrenal cortical hormones is present in diabetics with retinopathy, and in some way alters or masks the latent vitamin B_{12} defect of this group.[14, 23, 24]

In the present case, the short duration of known diabetes, its mildness, and particularly the advancement of the retinopathy following surgery in the absence of overt diabetes or even a diabetic glucose tolerance curve, would indicate that the factors of diabetic control, hyperglycemia, or duration of symptoms had no importance in the development of diabetic retinopathy. It is suggested that the suddenly advancing diabetic retinopathy in this case was related to the transient elevated levels of adrenocortical steroids during surgery and the postoperative period, for the following reasons:

1. The flare-up of retinopathy postoperatively occurred abruptly during a period of stress and relative hyperadrenocorticism.

2. Concurrent postoperative thrombophlebitis probably prolonged this period of stress-induced hyperadrenocorticism.

3. Resolution of the diabetic retinopathy occurred gradually following abatement of the period of stress.

4. Advancement of diabetic retinopathy during periods of stress has been previously reported.[18, 22]

5. The fact that these retinal changes are not observed in normal individuals postoperatively suggests that pre-existent secondary diabetes mellitus in some way altered this patient's retinal vascular response to elevated blood levels of adrenocortical steroids.

It is regretted that the inadvertent loss of postoperative blood and urine specimens for hormonal assay deprived us of laboratory substantiation of this hypothesis.

Conclusions and Summary

1. A case of pheochromocytoma and diabetes mellitus is reported, with amelioration of all laboratory evidences of diabetes following extirpation of the tumor. Despite the absence of diabetes mellitus postoperatively, rapidly advancing but transient diabetic retinopathy was noted.

2. A hypothesis for the pathophysiology of the postoperative retinal changes is offered.

Acknowledgment

We are indebted to Edmund B. Spaeth, M.D., Chief Surgeon, Wills Eye Hospital, Philadelphia, Pennsylvania, for his evaluation of the retinal findings in this case.

Summario in Interlingua

Es reportate un caso de diabete mellite secundari a pheochromocytoma, con melioration de omne le indicios laboratorial de diabete post le extirpation del tumor. In despecto del absentia post-operatori de diabete mellite, rapidemente progressive sed transiente retinopathia diabetic esseva notate. Ben que diabete mellite es trovate frequentemente in association con pheochromocytoma, in tanto que le autor lo sape, retinopathia diabetic ha non previemente essite reportate in association con iste tumor. Es opinate per multe autores que le apparition de retinopathia diabetic es secundari a influentias hormonal plus tosto que al duration o al tractamento del diabete mesme. In le presente caso, le breve duration del diabete in tanto que illo esseva documentate, le leve grados de illo, e particularmente le progresso del retinopathia post le chirurgia e in le absentia de diabete pare arguer contra le these que le tractamento de diabete, hyperglycemia, o le duration del symptomas esseva factores de importantia in le disveloppamento del retinopathia diabetic. Es opinate que le subite progresso del retinopathia diabetic in iste caso esseva relationate con le elevation transitori del nivellos de steroides adrenocortical durante le chirurgia e le periodo post-operatori.

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EPIDEMIC PLEURODYNIA, ORCHITIS, AND MYOCARDITIS IN AN ADULT DUE TO COXSACKIE VIRUS, GROUP B, TYPE 4*

By NAT H. SWANN, M.D., *Chattanooga, Tennessee*

SINCE the first of the Coxsackie viruses was isolated in 1948, at least 23 group A types and five group B types have been recognized, and many have been associated with diverse human diseases. The group B viruses have been implicated in a variety of disorders, ranging from epidemic pleurodynia to aseptic meningitis and pericarditis. Orchitis has been a less frequent compli-

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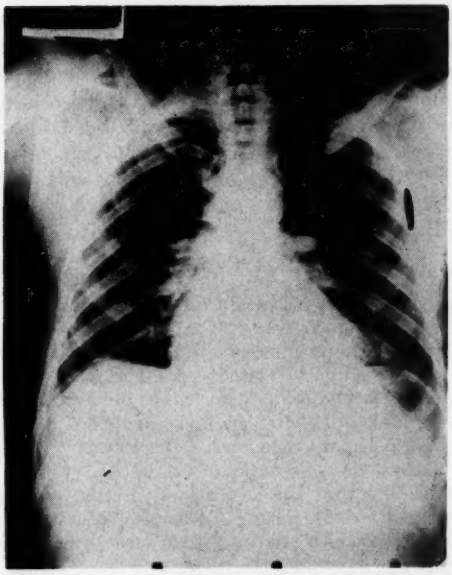

FIG. 1. Chest x-ray, July 30, 1959, showing enlargement of the heart and tenting of the right diaphragm.

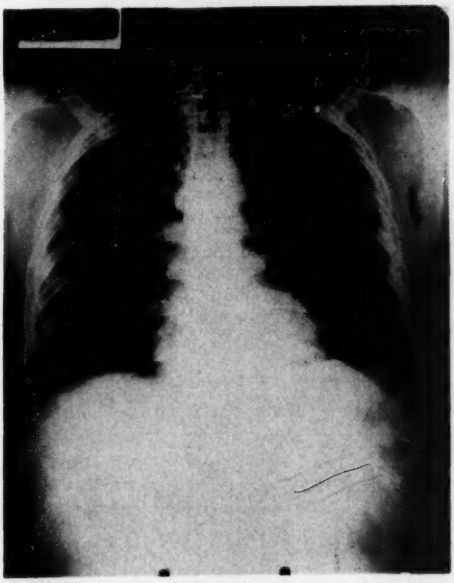

FIG. 2. Chest x-ray, August 11, 1959, showing the heart to be of normal size. Tenting of the right diaphragm has disappeared.

cation of epidemic pleurodynia. Infection with the group B viruses in the past has been associated with myocarditis during the neonatal period.[1] However, data are accumulating which suggest that unexplained occurrences of myocarditis and pericarditis beyond the neonatal period are due to these agents.[2, 3] Bell et al. have reported a case of pericarditis in an adult [4] due to Coxsackie virus, group B, type 3. Group B, type 5 has been implicated recently in myocarditis and pericarditis in the adult.[5, 6] The case presented below is one of Bornholm disease complicated by orchitis, with evidence of myocarditis in the adult due to Coxsackie virus, group B, type 4.

Case Report

This 28-year-old white male developed acute onset of severe, stabbing right chest pain on July 27, 1959. The pain was markedly accentuated on deep inspiration. Generalized malaise was present on admission to the hospital on July 30, 1959. Slight cough was present, but no sputum was produced. The patient was afebrile, and the physical examination was essentially negative except for a right pleural friction rub; no pericardial rub was heard. Laboratory studies revealed a white blood count of 8,750/cu. mm., with 68% polymorphonuclears. Chest x-ray on July 30, 1959, showed cardiomegaly, with a cardiothoracic ratio of 16 to 29.2 (Figure 1). There was tenting of the right diaphragm. The patient was treated with acetylsalicylic acid and codeine, and remained afebrile during his hospital course. Initially he received broad-spectrum antibiotics, which were discontinued later. The pain gradually

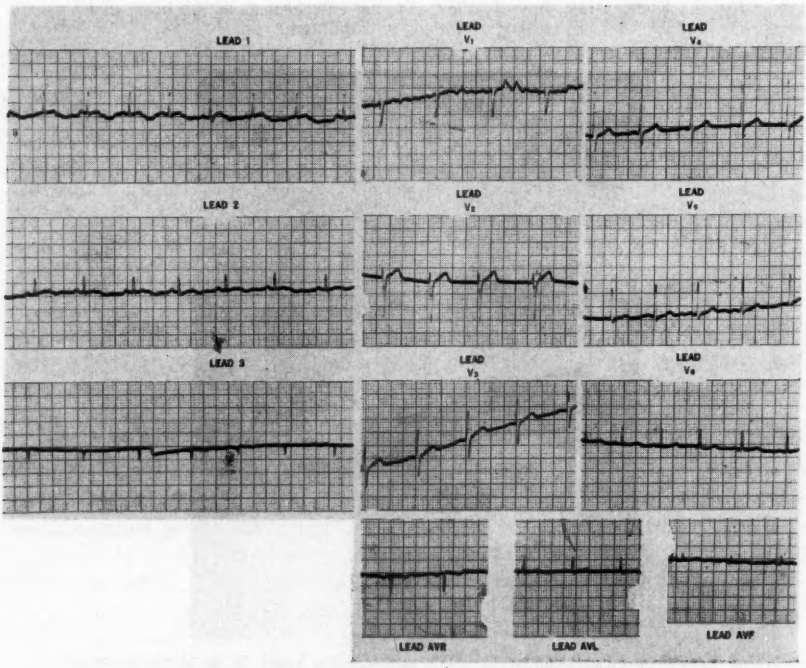

Fig. 3. The electrocardiogram shows changes consistent with myocarditis.

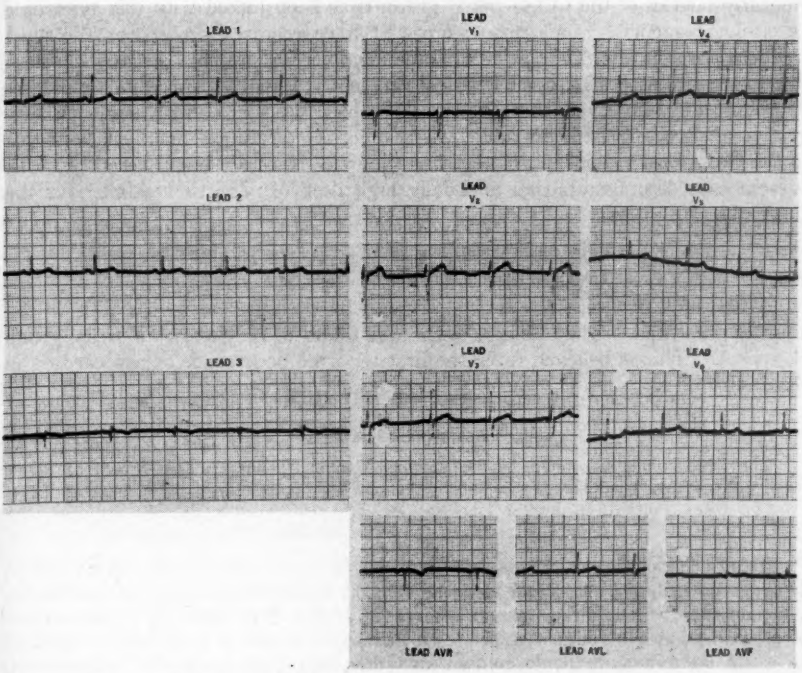

FIG. 4. The electrocardiogram has returned to normal two days later.

diminished, and he was discharged five days after admission. The chest x-ray on discharge was within normal limits.

One week later the patient was readmitted to the hospital with tenderness, swelling, and pain of the right testicle, and with recurrence of the knifelike pain in the right chest. Examination revealed no fever, but a bilateral pleural friction rub was present, with no pericardial rub being audible. Laboratory studies revealed a white blood count of 9,150/cu. mm., with 70% polymorphonuclears. The chest x-ray on August 11, 1959, showed no tenting of the diaphragm. The cardiothoracic ratio was 14.1 to 30 (Figure 2). The electrocardiogram showed T wave changes in standard Leads 1 and 2 and unipolar Leads AVL, AVF, and V_6 compatible with myocarditis (Figure 3). A wandering pacemaker was also noted. A repeat electrocardiogram two days later showed return of T waves to normal (Figure 4). The acute phase serum obtained on August 11, 1959, revealed neutralizing antibody titer of 1 to 256 for the Coxsackie virus, group B, type 4, and two weeks later convalescence serum revealed an antibody titer of 1 to 4,096. No attempt was made to isolate the virus. The patient was treated supportively, with codeine, salicylates, and elevation of the scrotum. He recovered uneventfully, and was discharged on the sixth hospital day of the second admission. He was seen two months later and no further symptomatology was noted.

DISCUSSION

Bornholm disease, first noted in 1872 in Norway, has been called Devil's Grip, epidemic myalgia, epidemic pleurodynia, and epidemic benign pleurisy.

Recently viruses of the Coxsackie B group have been linked with this syndrome as etiologic agents. Some investigators [7, 8] have reported orchitis as the most frequent complication. Interstitial inflammatory lesions of the myocardium due to the group B Coxsackie viruses were noted initially in newborn children. More recently, however, these agents have been associated with evidence suggestive of myocarditis in the adult. The diversity of clinical manifestations due to the Coxsackie viruses, particularly to group B, has been noted recently. The present case demonstrated an unusually high titer (1:256 to 1:4,096) for the Coxsackie group B, type 4 virus.

Summary

A case of Bornholm disease complicated by orchitis and myocarditis in the adult is presented. The etiologic agent was found to be Coxsackie virus, group B, type 4. This is believed to be the first reported occurrence of myocarditis in the adult due to group B, type 4 of the Coxsackie viruses.

Acknowledgment

The viral studies were done by the Virology Section, Tennessee Department of Public Health, Nashville, Tennessee.

Summario in Interlingua

Depost le isolation del prime representantes de virus Coxsackie in 1948, al minus 23 typos de gruppo A e cinque de gruppo B ha essite recognoscite, incluse multes associate con diverse morbos human. Virus de gruppo B es implicate in un varietate de disordines, ab pleurodynia epidemic ad meningitis aseptic e pericarditis. Orchitis ha essite un minus frequente complication de pleurodynia epidemic. Usque nunc, infection con virus de gruppo B esseva associate con myocarditis solmente durante le periodo neonatal. Tamen, un corpus de datos continua accumular se que suggere que inexplicate recurrentias de myocarditis e de pericarditis a etates in ultra del periodo neonatal es causate per iste agentes. Altere autores ha reportate pericarditis in un adulto, causate per virus Coxsackie, gruppo B, typo 3. Typo 5 de gruppo B esseva recentemente implicate in myocarditis e pericarditis in un adulto. Le hic-presentate caso es un caso de morbo de Bornholm, complicate per orchitis e con signos de myocarditis de adultos causate per virus Coxsackie, gruppo B, typo 4. Es opinate que isto es le prime reportate caso del occurrentia de myocarditis in un adulto causate per virus Coxsackie, gruppo B, typo 4.

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THE DEVELOPMENT OF THE NEPHROTIC SYNDROME DURING THE COURSE OF CONGESTIVE HEART FAILURE: CASE REPORT AND REVIEW OF THE LITERATURE *

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EDEMA and other signs of fluid retention may occasionally increase rather than regress during the course of treatment of congestive heart failure with mercurial diuretics. This lack of response to treatment may be related to the severe nature of the cardiac lesion. Recently, however, Burack et al.[1] have described four cases of congestive failure which they felt led to the development of the nephrotic syndrome, characterized by heavy proteinuria, hypercholesterolemia, hypoalbuminemia, and edema. While many cardiologists and students of nephrosis find no causal relationship between the two disorders,[2-13] the case presented here suggested such an association and prompted a review of the literature.

CASE REPORT

A 66-year-old white male was admitted to Peninsula Hospital on October 31, 1958, because of edema and dyspnea of two months' duration. He had first become ill in the summer of 1956, when he developed weakness, depression, cough, and slight dyspnea. Examination in November, 1956, showed an apical systolic and a blowing diastolic murmur along the left sternal border. *Streptococcus viridans* grew from three consecutive blood cultures, and diagnoses of rheumatic heart disease and subacute bacterial endocarditis were made. Laboratory studies showed a mild anemia, a normal urine except for 1-plus proteinuria, and a fasting blood sugar of 100 mg.%. A bacteriologic and clinical cure resulted from an intensive two-week course of penicillin and streptomycin, as serial blood cultures from December, 1956, through October, 1958, were all sterile.

During 1957 the patient had no signs of congestive heart failure, but in September, 1957, he developed auricular fibrillation, controlled by digoxin. However, in February, 1958, dyspnea, orthopnea, cervical venous distention, and râles developed. After several injections of Mercuhydrin during a one-week stay in the hospital the signs of cardiac failure disappeared. At this time the urine and serum proteins

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TABLE 1
Serial Laboratory Studies

Date	Urine					Blood	
	Sp. Gr.	Protein	RBC	WBC	Casts	BUN mg. %	Albumin/ Globulin Ratio
Aug. 1956		—	—	—	—	10	
11–24–56	1.027	1+	—	Rare	Occ. hyaline		
11–26–56	1.023	1+	0–4	4–6	—		
9–2–57	1.006	—	Rare	Occ.	—		
2–10–58	1.010	—	—	—	—	13.6	3.8/3.0
11–1–58	1.020	4+	0–2	2–4	2–4 granular & hyaline per LPF		1.6/2.8
11–5–58	1.013	4.4 gm./ 24 hr.	2 M/24 hr.	5 M/24 hr.	4.5 M/24 hr.*	25	2.2/3.1
11–10–58	1.007	4.1 gm./ 24 hr.	3 M/24 hr.	6 M/24 hr.	500,000/24 hr.	27	
11–17–58						31	
11–31–58		8.3 gm./ 24 hr.					

* Casts were granular and hyaline. There was no evidence of fatty degeneration. Their width varied from 12.5 to 25 μ. No oval fat bodies were observed.

The normal urinary 24-hour excretion of protein is 60 to 90 mg.; red blood cells, 1,000,000; white blood cells 2,000,000/cu. mm.; casts, 100,000.[42]

were normal; the protein-bound blood iodine was 5.4 μg.%. The heart had enlarged somewhat by x-ray since 1956.

Clinical improvement continued over several months, and from March to September, 1958, the patient took Neohydrin (chlormerodrin), one 40-mg. tablet daily. Edema and dyspnea began in September and progressively increased during October, despite salt restriction, injections of Mercuhydrin or Thiomerin, 2 ml. twice weekly, and resumption of Neohydrin, one tablet daily. A heavy proteinuria was noted for the first time.

Past history revealed that the patient had had the usual childhood diseases, without complications. He denied previous joint pain or inflammation. A subtotal gastric resection had been performed in 1949 for a bleeding duodenal ulcer, and digestive complaints had not reappeared. A primrose dermatitis had bothered the patient 30 years before but had never recurred. There was no history of bee sting or poison oak sensitivity, throat infection, or allergic disorders. He was free from any urinary complaint. In the last few years his diet had been inadequate because of anorexia.

Physical Examination: On admission the patient was a thin, sallow man who was not dyspneic but who appeared to be chronically ill. The skin and mucous membranes were clear. A small white scar was present in his left fundus, unchanged since 1956. The cervical veins were not distended. The thyroid was not enlarged. The chest appeared to be emphysematous, but the lungs were otherwise clear. Blood pressure varied from 140/60 to 160/70 mm. Hg. The heart rhythm was totally irregular; a loud apical systolic murmur and a grade 2 diastolic murmur along the left sternal border were again heard. No visceromegaly was noted on abdominal examination. Marked pitting edema involved both legs, the sacrum, and the abdominal wall. The genitalia and rectum and the neurologic status were normal.

Laboratory Findings: The blood count revealed a packed cell volume of 41%; hemoglobin, 13.7 gm.%; white blood cell count, 7,300/cu. mm., with a normal differential. Serology was nonreactive. Serial studies referable to the patient's renal

lesion are to be found in Table 1. Antistreptolysin titer was 12 U. Lupus erythematosus preparation and heterophil agglutinins were negative. Blood chemistry showed the following: sodium, 139 mEq./L.; potassium, 5.1 mEq./L.; chloride, 110 mEq./L.; CO_2, 23 mEq./L.; serum cholesterol, 360 mg.%; serum creatinine, 0.9 mg.%. Quantitative urine culture disclosed no significant bacilluria.

X-ray examination revealed a normal intravenous pyelogram except for poor concentration bilaterally. Chest films showed signs of emphysema, mild cardiomegaly, and pleural reaction at both lung bases.

Serial electrocardiograms were taken and all showed auricular fibrillation and the pattern of right bundle branch block. Compared with the record of November 1, 1958, that of November 15 disclosed T wave inversion in Lead 3 and marked ST depression in V_{2-5}. By November 17 the small R in Lead 1 had become smaller, T was now inverted in AVF, and the ST depression in the precordial leads was less marked.

The patient's hospital course was one of continued edema, resistant to therapy. He received his final dose of Mercuhydrin on November 1. Medrol, 32 mg. daily, was begun on November 11. He remained afebrile. On November 15 he complained of severe chest pain radiating into his arms and associated with nausea and

FIG. 1. A representative glomerulus with normal cellularity and basement membrane. (Trichrome stain, × 2,000.)

FIG. 2. Glomeruli and tubules, showing a small amount of protein in the pericapillary spaces and in the proximal convoluted tubules. (H. and E. × 500.)

vomiting. Electrocardiograms suggested that this was due to an acute posterior myocardial infarction. The patient died three days later, following a sudden recurrence of pain.

Pathologic Examination: The autopsy was performed 26 hours after death. The significant findings were in the cardiovascular system and the kidneys. The heart was enlarged and dilated, weighing 640 gm. The immediate cause of death was a massive hemopericardium resulting from rupture of a posteroseptal myocardial infarct. The infarct was recent and secondary to a thrombosis of the left circumflex coronary artery, which was the preponderant artery supplying the posterior portion of the myocardium. Both the mitral and the aortic valves revealed changes of healed rheumatic valvulitis. The aortic valve was incompetent, and the mitral valve was thickened and scarred and had shortened chordae tendineae. In addition, the anterior cusp had a smooth-bordered circular defect, 5 mm. in diameter, extending through the cusp. This undoubtedly was the site of the bacterial endocarditis, which was now healed. There was a mural thrombus in the left atrium. Congestive failure was manifested by small amounts of fluid in the peritoneal (500 ml.) and pleural cavities (300 ml.), dependent edema, particularly noticeable in the retroperitoneal tissues, and by passive congestion in the lungs and liver.

The kidneys were large, the right weighing 225 gm. and the left 210 gm. The capsules stripped readily, leaving smooth surfaces except for a single depressed scar of healed infarction in each of the kidneys. The sectioned surfaces were pale and slightly bulging, and showed a good corticomedullary demarcation. The cortices averaged 7 to 8 mm. in thickness. The pelves and ureters were normal.

Histologic sections of several representative portions of each kidney were remarkably unaltered except for mild tubular degeneration and the presence of hyalinized glomeruli in the rare subcapsular scars that marked the zones of infarction. The remaining glomeruli had capillary tufts of normal cellularity and showed thin, delicate basement membranes, as demonstrated by para-aminosalicylic acid and trichrome stains. The pericapillary spaces often contained precipitated granular protein, as did the lumina of the proximal convoluted tubules, which were lined by plump cells with eosinophilic granular cytoplasm and vesicular nuclei. Scattered tubules revealed flattening of the epithelial cells and irregular spacing of the nuclei. The distal convoluted tubules were frequently lined by epithelial cells of variable height, and in some there was desquamation of the cells. Nuclear pleomorphism and irregularity of spacing were occasionally noted. The collecting tubules con-

FIG. 3. These tubules demonstrate cellular desquamation, irregular spacing, and pleomorphism of nuclei; precipitated protein is again present in the tubular lumina. (H. and E. × 2,000.)

tained moderate numbers of casts. The renal arteries showed only minimal sclerotic changes. The pelves were of normal thickness and were covered by normal mucosa. Representative microscopic sections may be seen in Figures 1 to 3.

Comment: This elderly man developed the nephrotic syndrome during a course of mercurial therapy for cardiac failure secondary to inactive rheumatic heart disease. There was no history of sensitivity to poison oak or bee sting, an allergic reaction which may result in nephrosis.[14, 15] His early reaction to primrose without subsequent recurrence makes this flower an unlikely etiologic possibility. The failure to find the characteristic lesion on pathologic examination would tend to exclude subacute bacterial endocarditis, intercapillary glomerulosclerosis, thrombosis of the renal vein or vena cava, amyloidosis, collagen disease, and glomerulonephritis as causes of nephrosis. In respect to his subacute bacterial endocarditis, the two normal urinalyses and the normal serum protein found after treatment of the infection would seem to minimize the importance of this disease in the pathogenesis of the renal lesion. Furthermore, Spain and King [16] demonstrated that antibiotic treatment of subacute bacterial endocarditis prevented the development of diffuse glomerulonephritis and decreased the incidence of focal embolic glomerulonephritis by 50%, either of which may follow the infection in 33% and 48% of untreated cases, respectively. Thus, congestive heart failure and mercurial diuretics remain the prime choices as a cause of this nephrotic syndrome.

Discussion

It would be worth while to differentiate, if possible, the renal abnormalities produced by congestive heart failure from those induced by mercurial diuretics. The nephrotic syndrome has appeared after the use of teething powders,[17] fulminate of mercury, ointment and vermifuge, all of which contain mercury.[18] However, in these cases the free ion may well have been responsible. The newer organomercurials are safer. Nevertheless, azotemia, proteinuria, cylindruria, and hematuria have followed the administration of mercurial diuretics.[19-27] On pathologic examination the tubules of these kidneys showed degenerative and regenerative changes, including necrosis, foci of calcification, cloudy swelling and variation in the size of the epithelial cells, while the glomeruli remained essentially normal.[20-25] Most of these patients had congestive failure, which in itself may produce urinary [28-30] and pathologic [31] abnormalities similar to those induced by mercury. Thus, it is difficult to determine the exact role played by cardiac failure and the mercurial diuretics. However, mercurial diuretics have undergone frequent and prolonged use without the development of the slightest evidence of renal toxicity.[23, 25, 32-36] In line with this, Coblentz et al.[37] showed that their parenteral administration did not increase the level of the nonprotein nitrogen or proteinuria in a carefully studied group of patients with congestive heart failure.

A review of the literature revealed 14 other well documented cases of congestive heart failure who developed the nephrotic syndrome during the course of treatment with mercurial diuretics (Tables 2 and 3).[1, 18, 38-40] Their principal features are analyzed in Table 4. All types of underlying heart disease are represented. The use of organomercurials preceded the onset of nephrosis by

TABLE 2

Clinical Data on Patients with Nephrosis and Congestive Heart Failure

Author	Case No.	Type of Heart Dis.	Age	Mercurial Diuretic Dose & Duration of Use Before Onset of Nephrosis	Duration of Nephrosis & Course	Blood			Urine			
						BUN mg. %	SA gm. %	SC mg. %	Protein gm./24 hr.	RBC	WBC	Casts
Burack, 1958[1]	1	HCD	50	Chlormerodrin, 3 tab. daily for 3 mo.	Over 2 yr. Edema disappeared though proteinuria persisted while mercurial treatment continued. Alive.	13–20	1.3–2.4	220–377	3–9	—	—	Occ. hyaline
	2	RHD	43	Mersalyl, 2 ml. q. wk. for 1¼ yr.; then mercaptomerin, 2 ml. q. wk. for 1 yr.	1 yr. Cardiac death 2 mo. after proteinuria disappeared.	Normal	2.2–3.4	683	3–10	—	—	—
	3	HCD	53	Mersalyl, 1–2 × wk. for 3 yr.	5 yr. Alive. Nephrosis seemed to disappear though mercurial treatment continued.	10–18	1.1–3.3	242–450	2–9	—	—	—
	4	Atrial septal defect	70	1 × wk. for 2 yr.	6 mo. Cardiac death.	11	1.4–2.1	212–357	1–9	—	—	—
Munck, 1956[18]	5	HCD	59	17 ml. Mersalyl & 30 ml. Thiomerin in 28 wk.	5 wk. Died of pulm. embolism.	C 0:9	3.1	375	14–20	—	Pyuria	Few (gran.)
	6	HCD	50	Thiomerin, 80 ml. in 38 wk.	Over 3 mo. Alive.		1.9	290	10–20	—	Few	—
	7	ASHD	79	Thiomerin, 77 ml. in 41 wk.	Over 4 wk. Alive.		2.9		7–8	—	Few	Few
Riddle, 1958[38]	8	ASHD	67	Mersalyl, 300 ml. in 3 yr.	3 mo. Died.	25–63	2.5	800	4+	—	—	—
	9	HCD	80	Neptal, 204 ml. in 3 yr. Mercloran, 1 tab. q. day for 12 mo.	2 wk. Died in peripheral circulatory failure.	37–61	1.5	470	15	Few	Few	Few
	10	Lues	67	Neptal. Thiomerin, 176 ml. in 3 yr. Mercloran, 660 tab. in 11 mo.	2 mo. Died suddenly.	13–43	2.9	440–525	3–16	—	—	—
	11	ASHD	67	Neptal. Thiomerin, 60 ml. in 4 yr. Mercloran, 112 tab. in 8 wk.	Over 8 mo. Alive.	15–23	2.5–4.2	285	35	—	—	—
	12	ASHD	61	Neptal. Mersalyl, 260 ml. in 14 mo.	Alive.	28	1.8	400	23	—	—	—
Burston, 1958[39]	13	ASHD	69	Mersalyl, 2 ml. q. wk. for 2 mo.	2 wk. Died.	21	1.5		11–35	—	—	—
Clenner, 1958[40]	14	HCD	66	Mercuhydrin.	Nephrosis disappeared 4 mo. after a course of dimercaprol. Cardiac death 8 mo. later.	14–27	1.1–4.8	170–470	8.6 gm./L.	—	—	—
Thayer, present report	15	ASHD RHD	60	Neohydrin. Mercuhydrin, Thiomerin, 8 mo.	2 mo. Died from myocardial infarction.	25–31 C 0:9	1.6–2.2	360	4.1–8.3	2.5 M per 24 hr.	5.5 M per 24 hr.	0.5–4.5 M per 24 hr. gran. & hyal.

Abbreviations:
HCD: Hypertensive cardiovascular disease.
RHD: Rheumatic heart disease.
ASHD: Arteriosclerotic heart disease.
BUN: Blood urea nitrogen (normal, 10 to 20 mg. %).
C: Serum creatinine (normal, 1 to 2 mg. %).
SA: Serum albumin (normal, 4 to 5 gm. %).
SC: Serum cholesterol (normal, 150 to 250 mg.%).

TABLE 3

Pathologic Studies on Patients with Nephrosis and Congestive Heart Failure

Author	Case No.	Pathologic Material
Burack, 1958[1]	1 2 4	Biopsy: patchy thickening of basement membrane. Autopsy: mitral valvulitis; protein in renal tubules. Autopsy: renal congestion; atrial septal defect.
Munck, 1956[18]	5	Histologic exam. of kidneys normal.
Riddle, 1958[38]	8 9 10	Autopsy: glomeruli normal. Cloudy swelling, hyaline droplet degeneration, necrosis, and fatty infiltration of tubular epithelium, primarily proximal convoluted. Epithelial regeneration (cases 8, 9, 10).
Burston, 1958[39]	13	Autopsy: coronary arteriosclerosis and I.V. septal defect; glomeruli essentially normal except for eosinophilic material in Bowman's space and an occasional "shrunken" glomerulus; necrosis, vacuolation, and fatty infiltration of tubules.
Clenner, 1958[40]	14	Autopsy: traces of tubular damage with regeneration. Glomeruli intact. Moderate renal hyperemia.
Thayer, present report	15	Autopsy: glomeruli essentially normal. Degenerative & regenerative changes in the tubules.

an average of 21 months (two months to four years), but the dosage was not excessive. Although azotemia (blood urea nitrogen, 21 to 63) appeared in eight, none was clinically uremic. In three of Burack's patients the renal lesion seemed to recede despite continuation of mercurial therapy, and in one instance cleared entirely.[1] Treatment of Clenner's case[40] with a short course of dimercaprol after stopping Mercuhydrin led to the disappearance of all nephrotic manifestations within three months. One of Riddle's patients improved on withdrawal of diuretics.[38] On all other occasions, evidence of nephropathy persisted. All of these patients suffered from serious cardiac disease, and eight died within six months of the onset of nephrosis. It is of interest that the urinary sediment showed but a slight increase in the formed elements and cells in less than 40% of the patients. This is usually the case in both nephrosis and cardiac failure. (The average urinary excretory rate was 2,700,000 red blood

TABLE 4

Principal Features of 15 Cases of Nephrosis and Cardiac Failure

1. Duration of mercurial therapy before onset of nephrosis: 2 mo. to 4 yr. (average, 21 mo.)
2. Incidence of azotemia: 8/13
3. Serum albumin less than 3.2 gm.%: 15
   a. Albumin less than 2.6 gm.%: 12
4. Serum cholesterol greater than 300 mg.%: 11/13
5. Proteinuria, 1 to 35 gm. per 24 hr. (average, 16): 14/15 (4+ in 1 case)
6. Abnormality of urinary sediment
   a. Hematuria: 2
   b. Pyuria: 5
   c. Cylindruria: 5
7. Status of patients following onset of nephrosis:
   a. 9 dead (8 in 2 wk. to 6 mo.; 1 in 1 yr.)
   b. 6 living (1 mo. to 5 yr.)
8. Renal lesion improved in 5, disappeared in 2
9. Pathologic studies (10)
   a. Normal kidney except for congestion: 3
   b. Glomerular abnormality: 1 (thickening of basement membrane)
   c. Tubular degeneration: 6

cells, 5,500,000 white blood cells, and 290,000 casts per 24 hours in one study of heart failure.[30]) The only discrepancy is the failure to find fatty casts and oval fat bodies, always present in nephrosis, and occurring in 40% of decompensated patients.[41, 42] Burack attributed the development of the nephrotic state to congestive heart failure, whereas Munck, Riddle, and Burston incriminated the mercurial diuretics.

It is worth while to mention several similar cases that are delineated in less detail than the above. Derow and Wolf reported a fatal case of a 59-year-old woman who developed renal insufficiency, albuminuria, anasarca, low serum proteins, and hypercholesterolemia following administration of Mercupurin.[43] The nephrotic syndrome terminated in uremia and death in the two patients described by Preedy and Russell [44] and Waife and Pratt;[45] both showed severe degenerative changes in the tubules on autopsy. Similar pathologic findings are reported by Lederer in two patients treated with Salyrgan and chlormerodrin.[46] The case presented by Bruno should probably be excluded, because the patient also had diabetic intercapillary glomerulosclerosis.[47] In the pathologic study by Paul et al. of 50 patients with cardiac failure, they found three nephrotics, two of whom had never received mercurials (which had been given to 26 patients without the occurrence of a single instance of renal abnormality suggestive of toxicity).[31] Balslov reported two patients with nephrosis and bilateral thrombosis of the renal veins, both of whom were given mercurial diuretics for the treatment of heart failure.[48] Most of these authors implicated the organomercurials in the pathogenesis of the nephrotic syndrome, although Squire et al. noted three patients with cardiac failure in their collection of 44 cases of nephrosis,[49] and Kark et al. mention it as a cause in their recent complete review.[50]

Proteinuria and edema are prominent features of both congestive heart failure and nephrosis. It is difficult to determine whether similar mechanisms are operative among these patients, afflicted as they are by both disorders, and perhaps by mercurial intoxication. A possible correlation is found in the pathologic study of 50 cases of cardiac failure by Paul et al., who discovered three instances of membranous and two of focal glomerulonephritis.[31] Renal vasoconstriction,[51] elevation of renal venous pressure,[52] and a tubular defect [30] have all been implicated in the commonly occurring proteinuria of cardiac failure,[30, 53] while recent studies stress increased glomerular permeability [54–56] in the pathogenesis of nephrotic albuminuria, although decreased tubular reabsorption of protein may play a lesser role.[55] This concept is compatible with the anatomic findings of Allen,[57] Ehrich et al.,[58] and Bell,[5] who regularly describe an abnormality of the basement membrane of the glomerulus in nephrosis, in addition to the well-known degenerative tubular changes. Similarly, in both congestive failure and nephrosis, fluid retention has been ascribed to malfunction at the level of the glomerulus (decreased renal blood flow and glomerular filtration rate in cardiac insufficiency,[59] glomerulotubular imbalance in the nephrotic syndrome [60]), and to increased tubular reabsorption of salt and water,[61] related in part to excessive aldosterone activity.[9, 49, 62–66] In this particular group of patients it is impossible to tell which of these two factors, glomerular or tubular, is the more important, though it is noteworthy that pathologically the tubular lesions were very impressive and the glomerular were minimal. Apparently,

however, the use of mercurials and the presence of cardiac failure are both required for the development of this nephrotic syndrome.

From the practical standpoint, patients with congestive heart failure who receive mercurial diuretics should have periodic determinations of their 24-hour urinary protein excretion, blood urea nitrogen, and serum creatinine, especially if they are becoming more edematous despite treatment. If signs of the nephrotic syndrome are manifest, consideration should then be given to the use of steroids [67] and BAL after withdrawal of mercurials.

Summary

A case is presented of chronic congestive heart failure, treated with mercurial diuretics, who developed the nephrotic syndrome. Review of the literature disclosed 14 similar well documented cases. It is impossible to determine whether the organomercurials or some aspect of cardiac failure is responsible for the renal lesion.

Summario in Interlingua

Es presentate un caso chronic de congestive disfallimento cardiac, tractate con diureticos mercurial, in que se disveloppava le syndrome nephrotic, manifeste in forte proteinuria, hypercholesterolemia, hypoalbuminemia, e edema. Un revista del litteratura revelava 14 simile, ben-documentate casos. Typos arteriosclerotic, hypertensive, luetic, congenite, e rheumatic esseva representate. Le uso de organomercuriales precedeva le declaration del nephrose per periodos de inter duo menses e quatro annos (con un valor medie de 21 menses). Le sedimento urinari monstrava un leve augmento del elementos formate e del cellulas in minus que 40 pro cento del casos. Cylindros grassiose e corpores oval de grassia non esseva notate. Azotemia appareva in octo. Le lesion renal se meliorava in cinque e dispareva in duo. Le prognose in iste patientes esseva grave. Novem moriva in inter duo septimanas e un anno, usualmente per complicationes cardiovascular. Studios pathologic demonstrava congestion renal, insimul con alterationes degenerative e regeneratori in le tubulos, durante que le glomerulos remaneva essentialmente normal, con le exception de un caso de spissification del membrana basal.

Le mechanismos responsabile pro le proteinuria e le edema in iste patientes non es clar, viste que tanto disfallimento cardiac como etiam nephrosis esseva presente. Vasoconstriction renal, elevation del tension reno-venose, e un defecto tubular—omne istos ha essite incriminate in le albuminuria de congestive disfallimento cardiac, durante que augmento del permeabilitate glomerular es probabilemente plus importante que le reducite reabsorption tubular de proteina como causa del proteinuria de nephrosis. In ambe iste conditiones, le retention de liquido ha essite ascribite a un augmento del reabsorption tubular de sal e aqua si ben como a anormalitates glomerular (i.e. reducite fluxo de sanguine renal e relentate filtration glomerular in insufficientia cardiac e imbalancia glomerulo-tubular in nephrosis). Viste que le diureticos mercurial pote causar augmentos del excretion urinari de albumina, cellulas, e cylindros in association con alterationes degeneratori e regenerative in le tubulos renal, lor rolo in le pathogenese de iste syndrome debe esser prendite in consideration.

Ab le puncto de vista practic, patientes con congestive disfallimento cardiac sub tractamento con diureticos mercurial deberea esser subjicite periodicamente a determinationes de nitrogeno de urea in le sanguine e del excretion de proteina in urinas de 24 horas. Si signos de nephrosis se manifesta, le uso de steroides e anti-lewisito britannic, post le cessation del organomercuriales, debe esser prendite in consideration.

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EDITORIALS

HYPERCALCEMIA—DOUBLED CAUSES AND A DILEMMA

TWELVE years ago, Albright and Reifenstein set forth most of the now-known clinical causes of hypercalcemia in their monograph [1] on metabolic bone disease. Since then the list (Table 1) has grown only by the addition of "hyperthyroidism" and "neoplasm without skeletal lesions." Even the latter cause was anticipated by Albright in his case 5, "Hypernephroma with solitary metastasis to bone simulating hyperparathyroidism." But diagnosing the cause of an elevated serum calcium level has become an increasingly

TABLE 1

The Commonest Clinical Causes of Hypercalcemia

Primary hyperparathyroidism
Sarcoidosis
Hyperthyroidism
Neoplasm with skeletal lesions
Neoplasm without skeletal lesions
Immobilization with, for example:
  Paget's disease
  Paralytic poliomyelitis
Vitamin D intoxication
Milk-alkali syndrome
(Laboratory error)

complex problem in the past decade, due to the appearance of cases with less overt signs and symptoms and of cases with multiple causes for hypercalcemia.

One chemical test has been in vogue for the identification of primary hyperparathyroidism among these various causes of hypercalcemia, namely, the tubular reabsorption of phosphate (TRP), but the earlier hope has collapsed that this test would simply and unequivocally identify primary hyperparathyroidism from among other causes. Cases of primary hyperparathyroidism have shown normal values for the TRP, and low values appear in instances of hypercalcemia not due to this disease. This latter failure, of the false-positive type, is the more frequent. It is well illustrated in a recent case report; [2] a patient with hypercalcemia showed evidence to justify surgical exploration for a parathyroid adenoma. Among the abnormal chemical findings in this patient was a low value for the TRP, but the hypercalcemia was finally shown to be due to a renal-cell carcinoma

[1] Albright, F., Reifenstein, E.: Parathyroid glands and metabolic bone disease. The Williams & Wilkins Co., Baltimore, 1948, pp. 84–98.

[2] Case Records of the Massachusetts General Hospital: Case 9–1961. New Engl. J. Med. **264**: 242, 1961.

of the kidney, apparently without metastasis to bone. The differential diagnosis of hypercalcemia is still mainly a clinical, as against a laboratory, problem, demanding careful observation and reasoning.

The difficulty of the problem has been illustrated recently by reports of the ultimate discovery of primary hyperparathyroidism in patients also having other diseases known to cause hypercalcemia. In one case,[3] primary hyperparathyroidism was shown to be present in a patient with sarcoidosis only after the hypercalcemia was not suppressed by cortisone administration. In two cases of hyperthyroidism recently published in the ANNALS,[4] the hypercalcemia was not due simply to hyperthyroidism but to concomitant primary hyperparathyroidism. Two case reports in this present number of the ANNALS call attention again to the hazard in assuming that the identification of a non-parathyroid cause of hypercalcemia in a patient necessarily excludes the simultaneous presence of primary hyperparathyroidism. In the first case, reported by Kohn and Myerson,[5] a man with Paget's disease showed hypercalcemia shortly after he was admitted to a hospital and put to bed. Symptoms of hypercalcemia, polyuria and polydipsia, and intractable constipation, had preceded the fracture by many months; and the hypercalcemia persisted after the patient was out of bed. These facts led to the correct and finally-proved diagnosis of primary hyperparathyroidism. In the second case,[6] the persistence of hypercalcemia and attendant symptoms in a woman adequately treated for hyperthyroidism suggested the diagnosis of primary hyperparathyroidism, confirmed by removal of an adenoma. In these two cases, good clinical observation was the prerequisite to a finally-correct diagnosis of the cause of hypercalcemia.

A third case report[7] in this number of the ANNALS, an instance of severe hypercalcemia in the presence of minimal bone erosion due to a neoplasm, raises the question again of the cause of hypercalcemia in patients with neoplasms not extensively or demonstrably involving the skeleton. This problem was first raised by Albright in the case[1,8] of hypernephroma showing hypercalcemia with only a single metastasis to the pelvis. Albright considered that the tumor might be producing a parathyroid hormone-like substance, but Collip found no evidence of such activity in an assay of the

[3] Burr, J. M., Farrell, J. J., Hills, A. G.: Sarcoidosis and hyperparathyroidism with hypercalcemia. Special usefulness of the cortisone test. New Engl. J. Med. **261**: 1271, 1959.

[4] Bortz, W., Eisenberg, E., Bowers, C. Y., Pont, M.: Differentiation between thyroid and parathyroid causes of hypercalcemia. Ann. Intern. Med. **54**: 610, 1961.

[5] Kohn, N. N., Myerson, R. M.: Hyperparathyroidism associated with Paget's disease. Ann. Intern. Med. **54**: 985, 1961.

[6] Jackson, C. E., Webster, J. S., Talbert, P. C., Caylor, H. D.: Concomitant hyperparathyroidism as a cause of the hypercalcemia associated with hyperthyroidism. Ann. Intern. Med. **54**: 992, 1961.

[7] Stone, G. E., Waterhouse, C., Terry, R.: Hypercalcemia of malignant disease: case report and a proposed mechanism of etiology. Ann. Intern. Med. **54**: 977, 1961.

[8] Case Records of the Massachusetts General Hospital: Case 27461. New Engl. J. Med. **225**: 789, 1941.

tumor. When Connor et al.[9] described two cases of bronchogenic carcinoma in which the hypercalcemia regressed following surgical removal of the tumor, interest in this question was quickly revived. Shortly thereafter, Plimpton and Gellhorn [10] reported a similar sequence in one patient with a papillary adenocarcinoma of the ovary, and in two patients with clear cell carcinomas of the kidney. Subsequently additional instances of hypercalcemia with neoplasm without apparent or extensive bone metastases were reported; the types of tumors showing this picture are summarized in Table 2. One of the more recent reports [2] again describes relief from hypercalcemia following removal of the tumor.

TABLE 2

Cases of Hypercalcemia Due to Neoplasm without Apparent or Extensive Metastasis to Bone

Lung carcinomas		
	Connor, Thomas, and Howard[9]	2 cases
	Plimpton and Gellhorn[10]	2 cases
	MGH Case 43161[11]	1 case
	Gold and Shnider[12]	1 case
	Myers, W. L.[13]	1 case
Carcinoma of kidney		
	Plimpton and Gellhorn[10]	4 cases
	Alanis and Flanagan[14]	1 case
	MGH Case 9–1961[2]	1 case
Ovarian neoplasm		
	Plimpton and Gellhorn[10]	1 case
	Abouav, Berkowitz, and Kalb[15]	1 case
Other neoplasms		
Hemangiosarcoma of the liver	MGH Case 39061[16]	1 case
Endometrial carcinoma	Plimpton and Gellhorn[10]	1 case
Hodgkin's disease	Plimpton and Gellhorn[10]	1 case
Anaplastic carcinoma	Plimpton and Gellhorn[10]	1 case
Carcinoma of the bladder	Cited by Leaf[2]	1 case
Carcinoma of the pancreas (?)	Lucas[17]	1 case
Lymphosarcoma	Myers[18]	1 case
Carcinoma of the cervix	Stone, Waterhouse, and Terry[7]	1 case

The commonest explanation for the appearance of hypercalcemia in these cases has been that the tumor produces a parathyroid hormone-like substance,[2, 8–10] an explanation which may be derived from several types of

[9] Connor, T. B., Thomas, W. C., Jr., Howard, J. E.: The etiology of hypercalcemia associated with lung carcinoma. J. Clin. Invest. **35**: 697, 1956.

[10] Plimpton, C. H., Gellhorn, A.: Hypercalcemia in malignant disease without evidence of bone destruction. Amer. J. Med. **21**: 750, 1956.

[11] Case Reports of the Massachusetts General Hospital: Case 43161. New Engl. J. Med. **21**: 750, 1957.

[12] Gold, G. L., Shnider, B. I.: Some unusual syndromes associated with neoplastic disease. Ann. Intern. Med. **51**: 890, 1959.

[13] Myers, W. L.: Hypercalcemia in neoplastic disease. Arch. Surg. **80**: 308, 1960.

[14] Alanis, B. F., Flanagan, J. F.: Myopathy and hypercalcemia occurring with carcinoma of the kidney. J. A. M. A. **171**: 2076, 1959.

[15] Abouav, J., Berkowitz, S. B., Kolb, F. O.: Reversible hypercalcemia in masculinizing hypernephroid tumor of the ovary; report of a case. New Engl. J. Med. **260**: 1057, 1959.

[16] Case Records of the Massachusetts General Hospital: Case 39061. New Engl. J. Med. **248**: 248, 1953.

[17] Lucas, P. F.: Acute hypercalcaemia from carcinomatosis without bone metastasis. Brit. Med. J. **1**: 1330, 1960.

[18] Myers, W. P. L.: Hypercalcemia in neoplastic disease. Cancer **9**: 1135, 1956.

evidence. Removal of the tumor corrects the hypercalcemia; hence the tumor must be producing a responsible substance. Bone not involved by tumor may show evidence of excessive resorption, and notably osteoclastic resorption,[7, 11] a characteristic of hyperparathyroid bone disease. The serum phosphorus level may be low or low normal as in primary hyperparathyroidism, and the tubular reabsorption of phosphorus may be depressed.[2] The parathyroid glands are usually normal.[10, 16] However, many objections can be raised against this interpretation. Excessive resorption of bone, even including increased osteoclasis, is not necessarily a specific sign of hyperparathyroidism in bone. It appears in other clinical entities; it appears in cortisone-induced osteoporosis in rabbits[19] and may appear in some *older* strains of mice during estrogen treatment,[20] to cite only two experimental and clearly defined examples. Furthermore, slight depressions of serum phosphorus in these cases can be attributed to the reciprocal relation of serum calcium and phosphorus determined by the solubility product of bone salt, and the tubular reabsorption of phosphorus has been normal in at least one of these cases.[15] Cortisone or prednisone may depress the hypercalcemia, an effect not characteristic, so far, in primary hyperparathyroidism.[7, 17] Direct assay of tumors for parathyroid hormone activity has so far given negative results.[2, 8]

In two cases,[7, 11] the histologic appearance of parathyroid hyperplasia has suggested that the tumor may have been elaborating a parathyrotrophic substance which stimulated increased output of the hormone from the parathyroid gland. However, usually the parathyroid glands have been normal grossly and histologically.[2, 10, 12, 13, 16] In the case of Stone et al.,[7] in this number of the ANNALS, the depression of hypercalcemia by cortical steroids prior to subtotal parathyroidectomy and the time lag of six days in fall of serum calcium after the operation are evidence against a parathyroid hormone effect from the tumor, be it either direct or indirect. The terminal fall in the serum calcium level could be due to a decline in output of the hypercalcemic agent, whatever its nature, from the tumor itself, if the tumor developed extensive necrosis.[9] Furthermore, in two cases,[2, 14] removal of the neoplasm led to a fall of serum calcium to *below* normal (serum protein levels not reported). If the parathyroid glands had been stimulated to hyperplasia by a trophic substance from the tumor, presumably the serum calcium levels would have been let down gently to normal. The mild hypocalcemic levels seen in these two cases postoperatively suggest that the parathyroids had in fact been inhibited by the preoperative hypercalcemia.

In view of the confusing and contradictory evidence as to the nature of the hypercalcemic effect of these tumors, it is necessary to consider other possibilities. Plimpton and Gellhorn[10] suggested that "these tumors produce

[19] Storey, E.: Cortisone-induced bone resorption in the rabbit. Endocrinology **68**: 533, 1961.

[20] Silberberg, M., Silberberg, R., *in* The biochemistry and physiology of bone, G H. Bourne, Edit., Academic Press, New York, 1956, p. 644.

an abnormal substance which binds the calcium and transports it in excessive amounts," an example being the calcium-binding phosphate-rich lipoprotein which appears to be responsible for the hypercalcemia in egg-laying hens.[21] The degree of hypercalciuria which accompanies the hypercalcemia in these cases [11, 13, 15, 17] (in the absence of renal insufficiency) appears to be excessive, however, if increased binding by a non-filtered protein is the explanation for the hypercalcemia. The same authors [10] suggested that an increased estrogen effect on bone could be responsible. The estrogens are usually considered to promote bone formation, but in the appropriate experimental circumstances they may induce bone resorption.[20] Evidence in favor of hyperestrinism as a cause of the hypercalcemia has been cited in one case [16] but Plimpton and Gellhorn did not find endometrial changes in their cases consistent with this hypothesis.

The solution to this problem may be reached soon. Marsh and Walser [22] have found that patients with malignancy and hypercalcemia usually show increases in the complexed fraction of total plasma calcium while the percent of protein-bound calcium remains normal. The ionized fraction was unchanged in some cases and was increased in others. Of notable interest is their finding that the additional complexed fraction is filtrable and adds to the hypercalciuria, which disposes of the objection raised above to a hypothesis of increased calcium binding by a protein. Their finding may or may not be applicable to the cases cited in Table 2; seven of the eight patients had metastatic disease in bone. But one did not, as judged by ante-mortem evidence. That the complexing substance is produced by the tumors has not yet been shown.

The eventual answer may be that hypercalcemia in neoplasia without metastatic bone disease can be due to one or several of many possible mechanisms. The chief problem for the clinician at the present time is that neoplasms without apparent bone disease can be obscure and can mimic completely primary hyperparathyroidism.[2] At present the correct diagnosis in such cases can only be reached through careful clinical deliberation, but some day a clearer physiologic explanation of the neoplastic hypercalcemia in the absence of metastasis may help the physician to reach the proper diagnosis.

E. J. H.

WHY ABSTRACTS?

In this issue the Editors are initiating a policy of publishing in the Annals abstracts of papers presented at the current Annual Session of The American College of Physicians. Our reasons for doing so are two. First, such publication extends to all readers of the Annals who were not in

[21] Ericson, A. T., Clegg, R. E., Hein, R. E.: Influence of calcium on mobility of electrophoretic components of chicken blood serums. Science **122**: 199, 1955.

[22] Marsh, E. F., Jr., Walser, M.: Filtrable calcium complexes in the hypercalcemia of malignancy. Clin. Res. **9**: 205, 1961.

attendance a bird's-eye view of the scientific papers presented at the Annual Session. Second, the abstracts are placed on record in the permanent medical literature.

The first of these reasons needs no further justification, the second should be an added inducement to the investigators to submit for the program their newest and most important work. We do not wish to encourage the practice of bibliography building nor do we want to promote multiple publication of abstracts of the same piece of work. In a literature-laden world staggering under the onslaught of the printed page this practice cannot be condemned too severely! But it is legitimate and often useful to have a preliminary record of a scientific study that is presented later in the ANNALS or elsewhere as a full length paper, ripe in content and, we hope, in wisdom.

We regret that abstracts are not available of the papers given this year before the Basic Medical Science Sessions; we hope to have them next year. But we do give you those of the Morning Lectures, the Clinical Sessions, and the Clinical Investigation Sessions. The Program Committee is to be congratulated on having arranged such an outstanding and comprehensive program. All the readers of the ANNALS ought to know about it—hence the abstracts.

J. R. E.

ABSTRACTS

OF

SCIENTIFIC PAPERS PRESENTED AT THE FORTY-SECOND ANNUAL SESSION OF THE AMERICAN COLLEGE OF PHYSICIANS MIAMI BEACH, FLORIDA MAY 8–12, 1961

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* By invitation
(ML) Morning Lecture
(CS) Clinical Session
(CI) Clinical Investigation Session

Cardiovascular Disease

Enzyme Inhibitors in the Treatment of Hypertension. Brest, A. N., M.D.,* and Moyer, J. H., III, M.D., F.A.C.P., Philadelphia, Pa. (CS)

The use of enzyme inhibitors in the treatment of hypertension is currently being investigated. Several monoamine oxidase (MAO) inhibitors, including iproniazid and 1-phenyl-2-hydrazine propane, have demonstrated significant antihypertensive abilities. In addition, the hypotensive action of these compounds is further enhanced by the therapeutic addition of the thiazide derivatives. The MAO inhibitor nialamide was used alone and in combination with thiazide derivatives in 40 patients with significant antihypertensive results, and serious toxic or side reactions were not encountered. The mechanism of hypotensive action of the MAO inhibitors appears related, at least in part, to ganglionic blockade. More recently, decarboxylase inhibitors have been investigated in hypertensive subjects. Twenty patients were treated with alpha-methyl-3,4-dihydroxyphenylalanine and the antihypertensive effect of the latter drug was confirmed. The hypotensive action of the decarboxylase inhibitors appears to be due to the inhibition of the decarboxylation of dihydroxyphenylalanine to dihydroxyphenethylamine (dopamine). The subsequent synthesis of the sympathetic mediator, norepinephrine, is thereby reduced. In addition to their potential therapeutic usefulness, the enzyme inhibitors may ultimately provide additional insight into the pathogenesis of the hypertensive process.

Mechanisms of Quinidine Action on the Circulation and Therapeutic Reversal of Toxic Effects. Conn, H. L., Jr., M.D., F.A.C.P., Luchi, R. J., M.D.,* and Helwig, J. H., Jr., M.D.,* Philadelphia, Pa. (CI)

Despite wide recognition of the electromechanical cardiac depressant and vasodilating effects of quinidine, the basic mechanisms responsible are obscure. Equally obscure are the mechanisms responsible by which the commonly used therapeutic agents reverse these effects. Even the usefulness of some recommended therapeutic agents is in doubt. Our data and those of others, derived from perfused heart experiments, have indicated that cardiac depression may in great part be due to derangement in cation movements and distribution. Subsequent in vitro dialysis studies of quinidine-protein binding led us to suggest that there is a specific binding at the cell surface between quinidine, cell membrane, and adjacent water. As a result of this special molecular orientation of quinidine, cell permeability is altered, ionic derangements ensue, and demonstrable electrocardiographic changes develop. Reduced muscle contractile rate may result from a similar series of events. In corroboration, no cardiac electromechanical alterations were seen in intact dogs as a

result of infusing a quinidine homolog (4-hydroxymethyl 6-methoxyquinoline) which lacks the necessary configuration to form a protein-water bridge. This drug did produce vasodilatation, an action which is thereby considered due to the quinoline ring fraction of quinidine operating at a non-membrane site. The vasodilatation was shown to lead to hypotension on the basis of direct vascular drug action in competition with pressor amines. A satisfactory explanation is thereby provided for the known efficacy of pressor amines in treating quinidine toxicity. The conclusion was further corroborated in our reversion of toxic effects by adequate dosage of hypertensin and levarterenol. Previous studies had suggested that changes in ionic composition, especially through sodium lactate administration, would reverse quinidine effects. We studied both changes in hydrogen and calcium ion concentration. Versene infusions alone partially reversed the hemodynamic and electrocardiographic abnormalities, and nearly complete reversion was obtained by the combination of versene and pressor amines. In contrast, both decreasing pH by acid administration and increasing pH by administration of sodium lactate either failed to exert a favorable response or actually aggravated the toxic state.

"Mesenteric Vascular Insufficiency" in Myocardial Infarction, Cardiac Failure, Cardiac Arrhythmias, and Shock States. Corday, E., M.D., F.A.C.P., Beverly Hills, Calif., Irving, D. W., M.D.,* Los Angeles, Calif., Gold, H., M.D., (Assoc.), Beverly Hills, Calif., Bernstein, H., M.D.,* and Williams, J. H., M.D.,* Los Angeles, Calif.

Experimental and clinical evidence will be presented to explain ischemic changes in the gastrointestinal tract resulting from remote extra-mesenteric circulatory disturbances such as hemorrhagic and traumatic shock, arrhythmias, myocardial infarction, and cardiac decompensation. The blood flow of the mesenteric circulation was measured during the various pathological states with the new accurate electromagnetic flowmeter and electronic integrator-computer. The mesenteric circulation decreases markedly during shock states, cardiac arrhythmias, and congestive heart failure. The resistance of the mesenteric circulation increases considerably due to a vasoconstriction. This results in ischemia and necrosis of the gastrointestinal tract. Findings at autopsy have been correlated with direct measurements of the mesenteric circulation in the laboratory. Mesenteric ischemia could account for the symptoms reported in patients with the above conditions. The term "mesenteric vascular insufficiency" is proposed as a descriptive term to explain the clinical entity.

Primary Myocardial Disease. Fowler, N. O., M.D., F.A.C.P., Gueron, M., M.D.,* and Rowlands, D. T., Jr., M.D.,* Cincinnati, O. (CI)

This study describes 19 patients with congestive heart failure without clinical or pathologic evidence of a primary cause. Eighteen patients were autopsied; one had left ventricular biopsy at thoracotomy. Their ages were from 18 months to 68 years at death. Seven patients had heart failure for five years or more; three had heart failure for over 10 years. Seven patients were alcoholic and three had nutritional cirrhosis. Transient mitral or tricuspid systolic murmurs and apical protodiastolic gallop rhythm were common. Atrial fibrillation was present in seven patients. The electrocardiograms revealed abnormal left axis deviation in five and left bundle branch block in two.

Right heart catheterization in five patients showed low cardiac output, increased arteriovenous oxygen difference, and elevation of pulmonary arterial, pulmonary wedge, right ventricular diastolic, and right atrial pressures.

At autopsy, heart valves and pericardium were normal. There was no significant coronary arteriosclerosis. Nephrosclerosis was absent. Heart weights exceeded 500 gm. in 13 patients. All 18 who were autopsied had left ventricular hypertrophy. Mural thrombi were present in 11; five had pulmonary emboli and five had systemic arterial emboli. No patient had gross myocardial scarring or evidence of myocarditis. Ten had focal increases of elastic tissue.

Primary myocardial disease may simulate coronary artery disease because of the abnormal electrocardiogram; hypertensive heart disease because of elevation of diastolic blood pressure during heart failure in some patients; or pericardial effusion because of poor cardiac pulsations, narrow pulse pressure, and paradoxical pulse. It may mimic rheumatic heart disease because of systolic murmurs, apical diastolic gallop, or murmurs on physical examination, and left atrial enlargement and Kerley lines on roentgen examination. The cause is unknown. Only one patient had a familial history of similar heart disease.

Abstracts of the papers given in the Basic Science Session are not included.

Newer Advances in the Pathogenesis of Human Hypertension: The Adrenal Cortex and Renal Pressor Mechanism. Genest, J., M.D., F.A.C.P., Biron, P., M.D.,* Koiw, E.,* Nowaczynski, W.,* Boucher, R.,* and Chrétien, M., M.D.,* Montreal, Que. (CI)

Recent studies from this laboratory have shown (1) an excessive fluctuation of daily urinary aldosterone in hypertensive patients, (2) a significant decrease ($p < 0.001$) in mean urinary pregnanetriol in groups of patients with essential, renal, and malignant hypertension, and (3) a urinary pregnanetriol/aldosterone ratio below the lower limits of normal range in 92% of hypertensive patients.

The possibility of a relationship between the renal pressor mechanism and the adrenal zona glomerulosa secreting aldosterone, as suggested by available experimental evidence, was explored. Forty experiments in normal volunteers and hypertensive patients were done with intravenous infusions (duration: 7 to 14 hours) of glucose 5% in water, valine-5-angiotensin II, epinephrine, norepinephrine, and neosynephrine. Prior to, during, and following these infusions, studies were made on urinary electrolytes, aldosterone, cortisol, cortisone, and their tetrahydro derivatives and on the free and conjugated 17-hydroxycorticosteroids. Subjects were kept on a fixed sodium and potassium intake (102 and 90 mEq./day respectively). Valine-5-angiotensin II infusions (given at a rate sufficient to maintain an increase in diastolic pressure of 30 mm. Hg above control levels) were accompanied by a fall in glomerular filtration rate (inulin or creatinine clearances), marked sodium retention, fall in Na/K ratio, a 2.5 to 10-fold increase in urinary aldosterone with a parallel rise in tetrahydro-aldosterone and a much less significant increase in urinary cortisol and tetrahydrocortisone. Infusions of glucose 5% in water, norepinephrine, epinephrine, and neosynephrine were without any stimulatory effect on urinary aldosterone. Sodium excretion was markedly increased during norepinephrine and neosynephrine infusions. In contrast, angiotensin infusions to hypertensive patients produced an increased urine volume and sodium excretion, thus confirming Peart's experiments. These studies suggest (a) a close relationship between sodium, aldosterone, and angiotensin, (b) a basic difference between normal subjects and hypertensive patients in response to angiotensin.

A Long Term Study of Cerebral Vascular Disease. Groch, S. N., M.D., (Assoc.), McDevitt, E., M.D.,* and Wright, I. S., M.D., F.A.C.P., New York, N. Y. (CS)

A study of cerebral vascular disease, utilizing the patients on the wards of the Second (Cornell) Medical and Neurological Services and the First (Columbia) Medical Service, has been in progress at Bellevue Hospital since July, 1956. The study group to date has seen 631 patients with the clinical picture of a stroke. From this group of patients, those who have passed a set of rigid criteria have been selected by a randomized selector system as either controls or patients treated with anticoagulant drugs.

This paper will detail the distribution of patients seen through December, 1960. The criteria for randomization will be described and that group of patients deemed suitable for the randomized study of anticoagulant therapy will be discussed in terms of hemorrhagic complications, recurrent thrombo-embolism, and mortality.

Thus far, there has been a trend indicating that anticoagulant therapy reduces both the incidence of and mortality from recurrent thrombo-embolism.

Tentative conclusions concerning the role of anticoagulant drugs in the therapy of cerebral thrombosis will be made in the light of the results of this study and the work of others.

On the Cause of Syncope and Sudden Death in Primary Pulmonary Hypertension. James, T. N., M.D., (Assoc.), Detroit, Mich. (CS)

Syncope and sudden death are common clinical features of primary pulmonary hypertension. A number of hypotheses have been proposed to explain these phenomena but none has been fully satisfactory. One discrepancy has been the uncommon appearance of these features in secondary pulmonary hypertension.

While studying the histopathology of the sinus node and its artery in a variety of diseases, a case of primary pulmonary hypertension was examined. The sinus node in this case was extensively infarcted. The sinus node artery was not only ruptured, but the media in all areas showed degeneration, both cystic and noncystic. More careful examination of the arteries in the lung, kidney, and the remainder of the heart revealed that similar changes were present in the arteries of all these organs, although these changes were most frequent

in the lung and right atrium. The small arteries of the lung additionally demonstrated the typical intimal hyperplasia. Re-examination of all the criteria for diagnosis of primary pulmonary hypertension in this case left no doubt of its accuracy.

Subsequent examination of the sinus node and its artery in two additional cases of primary pulmonary hypertension has confirmed these findings. They were not present in five cases of secondary pulmonary hypertension or in four cases of disseminated lupus erythematosus.

The clinical implications of what seems to be a specific lesion in the pacemaker of the heart in three patients with primary pulmonary hypertension are obvious.

Risk Factors in the Development of Coronary Heart Disease. Six Year Follow-up Experience—The Framingham Study. Kannel, W. B., M.D., (Assoc.), Dawber, T. R., M.D., F.A.C.P., Kagan, A., M.D., F.A.C.P., Revotskie, N., M.D.,* Framingham, Mass, and Stokes, J., III, M.D., (Assoc.), Boston, Mass. (CS)

Factors possibly related to the development of coronary heart disease were studied prospectively in a sample (ages 30–59) of a town's population. One hundred eighty-six individuals (125 men and 61 women) developed manifestations of coronary heart disease (36.3 per 1,000) during six years' observation following the initial examination of the 5,127 subjects initially free of such manifestations.

In the age range of 30–44, there were 34 cases, with a male: female incidence ratio of 13–1; in the age range 45–62 the ratio in 152 cases decreased to approximately 2: 1.

Men had more serious diseases than women but incidence rates for angina were about equal in the sexes. Sudden death was approximately four times and myocardial infarction twice as common among men as among women. Angina pectoris alone occurred in 30% of the men and in 70% of the women with coronary heart disease.

Hypertension (greater than 160 systolic and/or 95 diastolic) was noted to be associated with almost a threefold increase in risk in men 40–59 years of age, and a sixfold increase in women the same age. Elevation of serum cholesterol levels (245 mg.% or more) was associated with more than a threefold increase in risk in men of this age range while contributing only slightly to increased risk among women. A pattern of left ventricular hypertrophy by electrocardiogram was associated with a two- to fivefold increase in risk of development of coronary heart disease in men age 40–59 years at elevated blood pressure levels.

Lipoprotein determinations offered no special advantages over the more simply and cheaply measured serum cholesterol determinations in assessing risk of development of coronary heart disease.

Combinations of these abnormalities of cholesterol, left ventricular hypertrophy, and hypertension further augmented risk. Men 40–59 years of age, normal with regard to these characteristics, had a six-year incidence of coronary heart disease of 35.8 per 1,000. When all three abnormalities were present, the incidence rose to approximately 500 per 1,000 (four out of eight). These risk factors occurred with sufficient frequency in the population to merit concern; 8% of men and 11% of women had two or more of these abnormal characteristics and at least one abnormal characteristic was present in approximately 40% of the population studied.

The Significance of Abnormal Arterial Pulse Waves in Diabetic Children. Lax, H., M.D.,* New York, N. Y., and Feinberg, A. W., M.D., F.A.C.P., Great Neck, N. Y. (CI)

We have previously reported abnormalities in the arterial pulse wave, recorded with a new cuff technic from the digits of human subjects, in adult patients with peripheral arteriosclerosis, with hypertension, or with diabetes mellitus. The major change noted is diminution to disappearance of the dicrotic segment of the arterial pulse wave.

This abnormality has now been found in diabetic children. One hundred ninety-eight diabetic subjects between the ages of 11 and 20 were examined. One hundred twenty-seven (64%) had abnormal arterial pulse waves, although none had clinical evidence of arteriosclerosis or hypertension. Only 14 abnormal cases (7%) were found in a control group of 205 non-diabetic subjects of the same age. The longer the duration of diabetes, the more likely pulse wave configurations would be abnormal. Although the median age was similar in the two groups, only one-half of 85 patients who had had diabetes less than five years showed abnormalities, whereas 76% of 77 subjects who had the disease longer than five years had abnormal recordings. Thirty per cent of 40 additional control subjects with a

positive family history of diabetes had abnormal pulse waves, although they were nondiabetic themselves.

This technic, which does not require arterial puncture, seems to offer a means of detecting changes in the arterial pulse wave configurations of diabetic children and in nondiabetic subjects with a positive family history of the disease that antedates clinical evidence of change in their vascular system. This supports the concept that diabetes is a multifaceted disease process where the carbohydrate and vascular aspects of the disease may progress independently of each other.

The Role of Pulmonary Compliance in the Predominance of Right Pleural Effusion in Congestive Heart Failure. Lepeschkin, E., M.D.,* Burlington, Vt. (CI)

It is a common finding that in congestive heart failure pleural effusion is more extensive on the right than on the left side, if no local factors such as pleural adhesions are present to upset this relationship. Many explanations have been advanced to account for this behavior, but none of them are quite satisfactory. The explanation developed by the author is that because the heart is on the left side, the volume of the left lung is smaller than that of the right lung. This difference is even more pronounced in the presence of cardiac hypertrophy or dilatation, which usually accompanies congestive failure. The same amount of pleural effusion will accordingly cause a greater relative decrease of lung volume and of the negative intrapleural pressure on the left side than on the right side, and this in turn will discourage further accumulation of transudate on the left side. In order to test this hypothesis, the intrapleural pressure of both lungs was measured during the course of alternately injecting 20-ml. volumes of air into the respective pleural cavities, in fresh cadavers of patients with normal cardiopulmonary heart and lungs, and of those with heart failure. It was found that during injection of 40–100 ml. of air, the right and left intrapulmonary pressures decreased at approximately the same rate, but that further injection usually caused the negative intrapleural pressure to decrease more on the left than on the right side. This difference was greater and appeared earlier in patients with enlarged hearts.

Coronary Visualization: Indications and Clinical Correlation. Likoff, W., M.D., F.A.C.P., Philadelphia, Pa. (CS)

Recent advances in technic enable the coronary arterial circulation to be visualized by means of opaque radiographic material quite routinely. A correlation of this type of examination with the clinical patterns of patients known to have advanced atherosclerosis has been carried out in order to clarify its safety, its diagnostic usefulness and whether or not this form of examination can be of assistance in acute and chronic treatment.

The safety of the procedure was indicated by the fact that not a single mortality or serious morbidity occurred in 100 separate procedures.

Coronary arteriography appeared to have diagnostic limitations. In discrete instances immediately preceding the occurrence of a myocardial infarction coronary visualization appeared to be normal. This also was observed in patients with longstanding and serious electrocardiographic abnormalities.

From a prognostic standpoint the ability to visualize extensive collateral channels circumventing an occluded area or the demonstration of a recanalization of a known previously occluded arterial segment was accepted as a favorable sign. In many instances, however, these findings were not demonstrated in patients who had enjoyed full and long recoveries from a coronary occlusion.

The explanation for the paradoxes indicated above may rest with the improved technics of examination, which will better clarify filling defects in the terminal branches of the coronary tree. Until that time, however, coronary arteriography represents an important, safe diagnostic tool in the evaluation of unusual clinical patterns suspected of being due to coronary artery disease.

Angiocardiographic Study of Dissecting Aneurysm of the Aorta. Lyons, H. A., M.D., F.A.C.P., Greenfield, H., M.D.,* and McFetridge, J. S., M.D.,* Brooklyn, N. Y. (CS)

The clinical diagnosis of dissecting aneurysm has become significantly important within recent years. Today, with the growth of experimental and clinical vascular surgery, the diagnosis of dissection of the aorta is of the utmost necessity from a therapeutic standpoint. Successful surgical management has been reported from several clinics.

To establish any diagnosis an objective means is always best. For this reason the angiocardiographic demonstration is best and gives the most useful information for the surgical treatment.

Sixteen cases of dissecting aneurysm were studied by angiocardiographic technic. The salient features of the radiographic and angiocardiographic studies will be shown. These include the abnormal contours of the aorta, the luminal occlusion sign, and the extravascular opacification.

The significance of these findings for a surgical approach is of tremendous importance.

The Diagnostic Precision of Cardiac Catheterization and Cinefluorographic Technics in Congenital Heart Disease. McIntosh, H. D., M.D., (Assoc.), Whalen, R. E., M.D.,* Hernandez, R. R., M.D.,* Morris, J. J., M.D.,* and Sealy, W. C., M.D.,* Durham, N. C. (CI)

This report contrasts the diagnostic precision of cardiac catheterization technics with selective cinefluorography in 37 consecutive patients with suspected congenital heart disease and demonstrates the increased diagnostic precision gained by combining the technics in the individual patient.

The complete diagnosis was correctly determined preoperatively by combined study in 13 of the 14 patients operated upon. Neither technic completely diagnosed a cor triatiorium with anomalous pulmonary venous drainage. Of these 13 patients the precise diagnosis could be established solely by catheterization in 11 and solely by cinefluorography in eight. Catheterization studies failed to distinguish a coronary A-V fistula from other causes of a left-to-right shunt or to elucidate the type of pulmonic stenosis. Cinefluorography failed precisely to localize a patent ductus arteriosus (PDA) in three; a coarctation in one; and strongly suggested a primum atrial septal defect (ASD) in a patient with a secundum defect.

Four of the unoperated 23 cases are still incompletely diagnosed. Of the remaining 19 cases a definitive diagnosis was made by combined technics in every case. Catheterization alone established the diagnosis in 16 patients; cinefluorography alone in 18. Catheterization technics failed to demonstrate a coronary A-V fistula, PDA, and the specific type of pulmonic stenosis. Cinefluorography failed to differentiate an atrioventricular communis from an ASD.

This study demonstrates the difficulty of: (1) precisely localizing cinefluorographically the site of shunting through a PDA; (2) diagnosing a coronary A-V fistula by catheterization; (3) determining the type and/or presence of pulmonary stenosis by catheterization; and (4) technical problems of cinefluorography.

Three cases demonstrating the increased diagnostic precision attained by combining cinefluorography with cardiac catheterization will be presented.

Physiologic Evaluation of the Coronary Circulation in Coronary Disease and in Congestive Failure. Messer, J. V., M.D.,* Neill, W. A., M.D.,* Wagman, R. J., M.D.,* Levine, H. J., M.D.,* and Gorlin, R., M.D., (Assoc.), Boston, Mass. (CI)

Myocardial oxygen requirements (MqO_2) are supplied by the interaction of coronary blood flow (CBF) and myocardial oxygen extraction. Earlier studies have shown the relative constancy of myocardial O_2 extraction in various states (rest, exercise, hypoxia, anemia), so long as coronary blood flow reserve is unimpaired.

Forty-four patients were studied by coronary venous catheterization at rest and during exercise with measurement of coronary and systemic hemodynamics. Distinct patterns of myocardial O_2 supply were observed in various clinical states. In 22 normals the increased MqO_2 of exercise was supplied by increased CBF and resting levels of O_2 extraction (70%). In seven coronary artery disease (CAD) patients, resting CBF and O_2 extraction were normal, but the increased MqO_2 of exercise was supplied by progressively increasing O_2 extraction (+9%) and subnormal elevation of CBF. The blood flow deficit averaged 9 ml./100 gm./min., or 10% inadequacy in comparison with the controls. Seven congestive heart failure (CHF) patients with normal cardiac indices (CI) had normal rest and exercise CBF and O_2 extraction patterns. Eight CHF patients with low CI had increased coronary (+17%) and systemic (+26%) vascular resistances and increased resting O_2 extraction (+11%), suggesting coronary insufficiency at rest, although CBF reserve during exercise was normal without further increase in an already abnormal O_2 extraction. In the presence of normal CBF reserve on effort, this constantly increased myocardial O_2 extraction suggests active coronary vasoconstriction in the resting and exercising states and participation of the coronary circulation in the peripheral vasoconstriction of low output CHF.

These observations have permitted physiologic differentiation of the normal and organically diseased coronary circulation, and have demonstrated the existence of "functional" coronary insufficiency in low output CHF. The decreased O_2 saturation of coronary venous blood resulting from abnormal myocardial O_2 extraction in low output CHF and in CAD during exercise may adversely affect myocardial function, thus contributing to the symptomatology, electrocardiographic alterations, and deranged physiology in these states.

Arteriovenous Differences in Coagulation and Fibrinolysis in Normal Subjects and in Patients with Atherosclerosis. Naimi, S., M.D.,* Goldstein, R., M.D.,* and Proger, S., M.D., F.A.C.P., Boston, Mass. (CI)

The importance of blood coagulation-fibrinolysis equilibrium in determining the natural course of atherosclerosis has been subject to scrutiny for many years. Yet most of the data in the literature on coagulation and fibrinolysis as related to atherosclerosis are based on the findings in the venous blood.

A comparative arteriovenous study was therefore undertaken in a group of normal and a group of atherosclerotic subjects. Coagulation tests in general showed no significant arteriovenous differences in either group or between the two groups. Fibrinolytic activity, however, was almost uniformly lower in the arterial blood. This arteriovenous difference was statistically significant in both groups and highly so in the patients with atherosclerosis. Furthermore, the arteriovenous difference in fibrinolysis varied widely in different subjects to the extent that it was felt that in studies of fibrinolysis as related to atherosclerosis, venous findings may not be taken as a true reflection of the lytic activity in the arterial system where the mechanism conceivably plays a more significant role and therefore routine use of arterial samples in such studies should be seriously considered. The atherosclerotic group in general had a lower fibrinolytic activity in both the arterial and the venous blood than the normal group. This reduced activity was especially marked in a number of younger patients (ages 32–45) with occlusive disease of the peripheral arteries. No correlation was found between the level of serum cholesterol and fibrinolytic activity. The cause and possible significance of these findings are discussed.

Effects of Aminophylline on the Dynamics of Left Ventricular Failure. Pariser, S. M., M.D., (Assoc.), Sancetta, S. M., M.D., F.A.C.P., and Schwartz, H., M.D., F.A.C.P., Cleveland, O. (CI)

The favorable clinical effects of aminophylline in left ventricular failure are generally accepted. However, correlative physiologic data are scanty. Accordingly, the present study of the cardiopulmonary circulatory effects of intravenous aminophylline on the altered dynamics of left ventricular failure was undertaken. Particular emphasis was directed to the correlation of cardiac ouput and the left ventricular mean filling pressure. The pulmonary veno-capillary ("PC") pressure was used as the index of the left ventricular mean filling pressure.

Twelve patients with significant heart disease were studied. The etiologies included systemic hypertension, coronary heart disease, aortic and mitral valvular disease, and diffuse myocardial fibrosis. Clinical and hemodynamic evidence of left ventricular failure was present in eight of the 12 patients. The "PC" pressure and cardiac output determinations were obtained in rapid succession and in duplicate before and after aminophylline. All post-aminophylline circulatory studies were completed within 30 minutes.

Of the eight patients in left ventricular failure, five showed a marked and persistent reduction in the "PC" and pulmonary arterial pressures after the administration of aminophylline. The average "PC" pressure reduction was 8.9 mm. Hg, representing a 50% change from the average basal level. No correlation as to degree and direction could be drawn between the changes in the "PC" pressure levels and the cardiac outputs.

Increased venomotor tone and its adverse effect on the dynamics of congestive heart failure are well established. Our findings suggest that a primary reduction in pulmonary venomotor tone is an important and lasting factor in the clinical and hemodynamic effect of aminophylline in left ventricular failure. Some basic implications and practical applications of this study will be suggested.

The Lilly Lecture: Essential Hypertension. Incidence, Course, and Heredity. Platt, Sir Robert, M.D., P.R.C.P. (Lond.), Manchester, Eng. (CS)

As knowledge increases of the causes of secondary hypertension (for instance, renal artery stenosis), the group of cases which remains in the category of essential hypertension

becomes more homogeneous and easier to define with regard to its incidence, behavior, and inheritance.

Available evidence on the incidence of essential hypertension suggests that it is less common in the population than some authors have made out. The question of whether a definition of normal and abnormal ranges of blood pressure can yet be made will be considered.

The behavior of blood pressure in the middle-aged population will be examined, particularly with a view to determining whether a group with essential hypertension can be clearly separated in this respect from the normal population.

A re-examination of the role of heredity in hypertension is being made at the present time, with special reference to the blood pressures of the siblings of persons with essential and with secondary hypertension.

Finally, some evidence will be presented on the role of the toxemia of pregnancy in the subsequent development of hypertension.

Problems in the Diagnosis of Angina Pectoris. Resnik, W. H., M.D., F.A.C.P., Stamford, Conn. (ML)

In the majority of cases the diagnosis of angina pectoris is simple, for the clinical picture corresponds closely with that described by Heberden in his classic article. The more puzzling cases fall into two categories. In the first, the difficulty comes from the inability or failure, be it conscious or unconscious, of the patient to describe his symptoms accurately. In the second are included those instances of angina pectoris in which the symptoms are truly atypical, either because of an unusual quality or location or reference of pain, or because the pain is unrelated to exertion. The appearance of pain at rest introduces the question of myocardial infarction, and the estimation of the serum transaminase level has proved to be invaluable in determining whether or not myocardial necrosis has occurred. The widely accepted concept that abnormality consists of a transaminase level about 40 units and that the peak level is attained within 24 to 48 hours requires modification.

Hydraulic Mechanisms in Endocarditis. Rodbard, S., M.D., F.A.C.P., Buffalo, N. Y. (CI)

Analyses of pathologic findings in infective endocarditis, as well as of hydraulic and bacteriologic studies, suggest that this process occurs only at sites where high pressure gradients extrude blood at high velocities through narrow orifices. Thus, involvement occurs only on the ventricular surfaces of insufficient aortic valves, on the atrial surfaces in mitral insufficiency, and beyond the narrowings of coarctations and of arteriovenous fistulae. Initial vascular injury is not a prerequisite. Endocarditis never occurs at large openings, such as atrial septal defects or a widely patent ductus, since the pressure gradient is not present and high velocities do not occur. High velocity flow probably produces its effects because it reduces lateral pressure locally, eliminates normal perfusion from lumen to intima, and causes retrograde perfusion of the lining of the vessel (Amer. Heart J. 51: 926, 1956). Oxygen, substrates, antibiotics, etc., therefore are not perfused through the site even though they may be present in abundance in the immediately adjacent arterial blood. This interpretation is supported by (1) animal experiments showing increased lipid infiltration above an induced stenosis and absence of infiltration at the narrowing; (2) experiments on deformable tubes in which the rates of deposition and of chemical reaction are affected by the velocity of the stream; (3) modifications in the rate of growth of bacteria in a bacteria-seeded agar tube with a coarctation-like constriction. These considerations suggest that hydrodynamic factors determine many of the special characteristics of endocarditis.

The Effect of Digitalis on the Cardiac Output of the Normal Heart at Rest and During Exercise. Rodman, T., M.D., (Assoc.), Gorczyca, C. A., M.D.,* and Pastor, B. H., M.D., F.A.C.P., Philadelphia, Pa. (CI)

Although it is generally stated that digitalis reduces the cardiac output of the normal heart, the experimental basis for the statement is questionable. The available data are sparse and contradictory because, until recently, determinations of the cardiac output required catheterization of the pulmonary artery and application of the Fick principle, a technically difficult and time-consuming procedure which is not readily reproducible.

A study was therefore undertaken utilizing a highly standardized dye dilution technic for the measurement of cardiac output. Sixteen normal young adult men were studied. The cardiac output, heart rate, stroke volume, minute ventilation, oxygen uptake, CO_2

production, and respiratory quotient were determined with each subject in a basal state and repeated during steady state exercise. Curves were constructed relating changes in cardiac output to changes in oxygen uptake and changes in arteriovenous oxygen difference.

In four subjects the resting and exercise studies were repeated two hours after an intravenous dose of 1.2 mg. lanatoside C. In the other 12 subjects digitalization was accomplished over a two-day period with oral digoxin (2.5 mg.) and maintained with a daily dose of 0.5 mg. The resting and exercise studies were repeated after the subject had been receiving digitalis for seven days.

Analysis of our data indicates that digitalis does not change the resting cardiac output in normal subjects nor does it impair the cardiac response to exercise.

The Association of Musculoskeletal Manifestations and Giant Cell Arteritis. Scherbel, A. L., M.D., F.A.C.P., and Hazard, J. B., M.D.,* Cleveland, O. (CS)

Giant cell arteritis, in contrast to periarteritis nodosa, is usually considered to be a benign, self-limiting vascular disease of unknown etiology involving the temporal or other cranial arteries in elderly people.

The close relationship between periarteritis nodosa and rheumatoid arthritis or other connective tissue disorders is well known. The purpose of this report is to describe the frequency of musculoskeletal manifestations in 11 patients with proved giant cell arteritis.

Seven of the patients were women; ages ranged from 57 to 77 years. Prodromal symptoms occurred for from two to eight months before localizing manifestations of the disease appeared. These included weakness, weight loss, fever, chills, anorexia, and mental aberrations. Occipital myalgia occurred in all patients. Temporomandibular arthralgia was present in seven patients, and in three motion of the jaw was temporarily restricted. Five patients had pain and swelling of one or more joints: two developed classical, chronically progressive rheumatoid arthritis; the third patient had acute arthritis of one knee followed by iritis six months before the onset of severe, persistent headache; and the remaining two patients had transient polyarthralgia, bilateral carpal tunnel syndrome, and bilateral trochanteric bursitis with associated tenderness of the fascia lata.

Comparison with other forms of arteritis, characteristic laboratory findings, and the unique response to therapy are discussed.

Accelerated Thromboplastin Generation in Patients with Acute Peripheral Arterial Occlusion Complicating Arteriosclerosis Obliterans. Spittel, J. A., Jr., M.D., (Assoc.), Pascuzzi, C. A., M.D.,* Thompson, J. H., Jr., M.D.,* and Owen, C. A., Jr., M.D.,* Rochester, Minn. (CI).

Some patients with arteriosclerosis obliterans experience a chronic course; others have acute arterial occlusion. Previous investigators have suspected hypercoagulability of the blood as the cause of the acute thrombotic arterial occlusion, but methods consistently effective in demonstrating hypercoagulability have not emerged.

During normal blood coagulation, the generation of thromboplastin requires more time than all other phases of clotting combined. Accordingly, the thromboplastin generation test (TGT), designed to measure the rate of formation of thromboplastin and the amount formed under standardized conditions, was utilized in this study of patients with arteriosclerosis obliterans. To increase the likelihood of detecting any acceleration of clotting, we modified the thromboplastin generation test by increasing the dilution of the plasma reagent (retarded TGT).

When the rate of thromboplastin generation of 70 patients with arteriosclerosis obliterans was compared with that of normal controls, significant acceleration of thromboplastin generation was demonstrable in 34. It should be emphasized that such acceleration—from two to five times normal—was found in 31 (70%) of 44 patients who had sustained an acute arterial occlusion one day to three months previously. Acceleration of thromboplastin generation was uncommon, however, in patients with chronic arteriosclerosis obliterans, being found in only three (12%) of 26 patients. None of the normal controls demonstrated accelerated thromboplastin generation.

The acceleration of thromboplastin generation does not appear related to the presence of gangrene. It can be a phasic phenomenon, having disappeared in 3½ weeks in one patient; in another patient it persisted for 3½ years.

Subsequent studies have shown that the accelerator of thromboplastin generation is a protein, electrophoretically a beta globulin, present in plasma but not in serum. Acceleration of thromboplastin generation may account for the development of acute arterial occlusion in some patients with arteriosclerosis obliterans.

Prevention of Stokes-Adams Seizures by Reducing Plasma Potassium with Chlorothiazide. Tobian, L., M.D., (Assoc.), Minneapolis, Minn. (CS)

Seven patients with a long history of Stokes-Adams seizures were given chlorothiazide, enough to lower the plasma potassium at least 0.6 to 1.1 mEq./L. When this had been accomplished, the Stokes-Adams seizures were abolished. A good result was always obtained when the plasma potassium got as low as 3.8 mEq./L. The lessened incidence of seizures was not accompanied by any change in plasma pH even though the plasma bicarbonate rose slightly in some cases. Electrocardiographic tracings revealed several instances of decreasing heart block while on the treatment. The most striking improvement was a change from complete heart block to normal sinus rhythm during the course of therapy. Our eighth patient with seizures represents a treatment failure. When he first received chlorothiazide, his plasma potassium went down to 3.9 mEq./L. and he was free of attacks. While on the same dosage of chlorothiazide his potassium gradually rose to 4.5 mEq./L. and he began having attacks. His daily dose of chlorothiazide was subsequently raised to 2,500 mg. without bringing his potassium level below 4.4 mEq./L. and he continued to have seizures. He demonstrates that when the drug does not lower plasma potassium sufficiently, it does not prevent seizures.

Summarizing, patients with malfunctioning conduction tissue have no safety margin, and a temporary slight worsening of conduction will bring on a period of asystole with loss of consciousness. Chlorothiazide changes the ratio of extracellular to intracellular potassium in the conducting tissue only about 15 to 20%, but this is enough to improve conduction, increase the safety margin, and therefore prevent seizures.

Syndrome of Ruptured Chordae Tendineae. Uricchio, J. F., M.D., (Assoc.), and Nichols, H. T., M.D.,* Philadelphia, Pa. (CS)

Rupture of the chordae tendineae is generally associated with previous bacterial endocarditis, myocardial infarction, and in rare instances trauma. The present report deals with a group of eight patients, five of whom presented a history of previous rheumatic fever. The unusual pathology was discovered during open heart surgery for correction of mitral regurgitation. The heavier cords which run from the ventricular surface of the cusps at varying distances from the free margins were those involved. In five cases, the chordae arising from the posterior papillary muscles and attached to the posterolateral half of the anterior septal leaflet were torn. "Flail" valve action resulted.

The clinical syndrome is reviewed and contrasted with that encountered in the usual form of rheumatic mitral regurgitation in which disease of the cusps leads to the production of the leak. In both, long asymptomatic intervals are common before the appearance of dyspnea and fatigue. On cardiac auscultation, a pansystolic rough apical murmur is common and the first heart sound and opening snap are not identified. The radiation of the murmur has a definite relationship to the location of the pathology and to the direction of the regurgitant jet. Chest x-ray demonstrates a moderate degree of cardiac enlargement consisting chiefly of left ventricular hypertrophy and left atrial dilatation. The electrocardiogram revealed left ventricular hypertrophy in four patients and atrial fibrillation in three. Cardiac catheterization fails to reveal any abnormalities within the pulmonary vascular bed. Newer methods of quantitating mitral regurgitation, such as cardiac ventriculography and cineangiocordiography, are sometimes helpful in evaluating the syndrome. The surgical experience of this disease is briefly reviewed. Eight patients were successfully operated on and the long-term results are outlined.

Clinical Application of Indicator Dilution Curves. Yu, P. N., M.D., F.A.C.P., Rochester, N. Y. (CI)

This paper reviews our experience in the use of arterial and precordial indicator dilution curves inscribed in over 500 cardiac patients. It also presents some of the newer developments in theoretical aspects and experimental studies concerning indicator dilution technic in the diagnosis of various types of cardiovascular lesions.

In congenital heart disease, within certain limitations, the indicator dilution curve is reliable to detect left-to-right shunts and to localize right-to-left shunts. Patterns of the indicator dilution curves in various types of valvular heart disease may be predicted with reasonable accuracy according to the nature, site, and degree of the lesion and other related factors. Detection and localization of the intracardiac shunts or valvular insufficiency may be further enhanced by (a) employing multiple appropriately selected sites of injection and of sampling, and (b) intravenous infusion of specific pharmacologic agents to alter the total systemic resistance. Utilizing experimental data obtained from a mechanical model of the heart and from the acute studies in dogs, quantitation of valvular regurgitation may be reasonably made by simple mathematical formulae.

Estimate of pulmonary blood volume in patients with various stages of mitral stenosis by means of indicator dilution curves may define the differences of pressure: volume relationships in the left atrium and pulmonary veins which exist between the hypertrophied but undilated left atrium in sinus rhythm and the widely dilated left atrium in atrial fibrillation.

Precordial radioisotope dilution curves not requiring arterial blood sampling are being used to measure cardiac output and "pulmonary" blood volume in many cardiac patients. Particular attention is centered on the day-to-day changes of volume-rate of blood flow in patients with congestive heart failure and in those with acute myocardial infarction. From such studies one is able to obtain useful information regarding more precise prognostication and more appropriate management of these conditions.

Endocrinology-Metabolic Disease

Hand-Schüller-Christian Disease: A Detailed Clinical Survey. Results of Short Term Prednisone Therapy in Ten Patients. Avioli, L. V., M.D.,* Lazor, M. Z., M.D.,* Kashima, H. K., M.D.,* and Andrews, J. R., M.D.,* Bethesda, Md. (CS)

Ten patients with the systemic variety of Hand-Schüller-Christian disease (eosinophilic xanthomatous granulomatosis) have been followed for periods of six to 18 months. Osteolytic lesions were observed in all patients; four presented with diabetes insipidus and three with exophthalmos. Seborrheic dermatitis, chronic otitis media, a non-regenerative anemia, and hepatosplenomegaly were also observed clinically. One case presented with exanthoma disseminata and what appeared to represent hypothalmic involvement, since the disease process was manifested by documented deficiencies in adenocorticotropic and thyroid-stimulating hormones. Bone age as well as urinary gonadotrophin levels were normal in this patient. Osteolytic lesions were biopsied and cultured before and after therapy.

Therapy consisted of the oral administration of from 50 to 60 mg. of prednisone daily for six weeks. This resulted in documented reversal of the disease process. Exophthalmos, hepatosplenomegaly, seborrhea, osseous lesions, xanthoma disseminata, anemia, and chronic otitis media responded most favorably to the therapeutic program. The amount of Pitressin essential for adequate replacement therapy decreased in three patients and was finally discontinued in one during the course of therapy. A complete reversal of the diabetes insipidus was documented in one patient by detailed laboratory investigation. Lipid fractionation studies of bone biopsy material were also obtained before and after steroid therapy.

No clinical or laboratory complications consequent to excessive steroid therapy have been noted in any of the patients to date. The effectiveness of prednisone in reversing the course of Hand-Schüller-Christian disease is discussed with respect to the pathogenesis of the disease process and recent investigations wherein the effect of adrenal cortical steroids on lipid metabolism have been evaluated.

Current Concepts of Parenteral Fat Nutrition. Becker, G. H., M.D., (Assoc.), Chicago, Ill. (CI)

The development of a suitable fat emulsion for intravenous use has helped solve the problem of caloric deficiency which frequently exists in patients with inadequate oral nutrition. The use of intravenous fat has also provided an opportunity to study certain aspects of fat metabolism in various disease entities including diabetes mellitus and renal failure.

Intravenous fat tolerance tests were performed in 148 chronically ill patients infused with a 15% cottonseed oil emulsion in doses of 1 gm./Kg. over a 3½ hour period. Total lipid, triglyceride, nonesterified fatty acids, and electrolyte levels were determined during and following the infusion. A consistent decrease in plasma potassium occurred, even when hyperkalemia due to renal insufficiency was present. The mechanism of this fall and its possible therapeutic implications in renal failure will be discussed.

Considerable individual variability in clearing an infused fat lead was observed. While in general a direct relationship exists between the degree of cachexia and the rate of fat clearance, in pancreatic disease, cirrhosis, and poorly controlled diabetes fat clearance was delayed. The addition of heparin in diabetics with delayed clearing returned the curve to normal, even when insulin was withheld.

A concept of fat clearance is presented indicating that: (1) the clearing effect of heparin is independent of pancreatic influence; (2) the condition of the organism with respect to fat storage or mobilization will determine whether clearance is rapid or delayed; (3) a

reciprocal relationship may exist between the level of non-esterified fatty acids and the amount of clearing factor produced.

Fat Mobilization in Man. Bogdonoff, M. D., M.D., (Assoc.), Estes, E. H., Jr., M.D., (Assoc.), Friedberg, S. J., M.D.,* and Linhart, J., M.D.,* Durham, N. C. (CI)

The status of fat mobilization in man may be described in part by the pattern of change in serum-free fatty acids and in part by the pattern of disappearance of infused radioactive labeled fatty acids. Both of these technics have been employed in a series of studies which have permitted a characterization of the net transport of lipid in a variety of clinical situations. It is the intent of the presentation to review a group of these observations. They may be summarized as follows:

1. Fasting accelerates lipid transport from the adipose deposits.
2. Muscular exercise effects an immediate utilization of transport lipid, which is followed by marked increases in mobilization.
3. Responsiveness of the individual to a fat mobilizing stimulus such as infused catecholamines is modified in patients with hypopituitarism and hypothyroidism; replacement therapy in these deficiency states restores responsiveness.
4. Patients with the nephrotic syndrome demonstrate decreased fat mobilizing responsiveness; responsiveness of enhanced degree occurs following the infusion of serum albumin.
5. Acute interference with glucose utilization at the cellular level (by infusion of 2-deoxy-D-glucose) activates fat mobilization, the process appearing to be mediated by central and humoral pathways involving adrenal medullary secretion.

These studies, therefore, have provided experimental evidence that the process of fat mobilization in man is a dynamic, highly reactive system, modified by the energetic, arousal, and hormonal status of the individual.

An Adrenal Medullary Function Test. Brunjes, S., M.D.,* Hodgman, J. E., M.D.,* Nowack, J., M.D.,* and Johns, V. J., Jr., M.D., F.A.C.P., Los Angeles, Calif. (CI)

Although the adrenal medulla is not an essential organ, it is well known that it plays a role in the regulation of blood sugar through the effect of epinephrine on glycogenolysis. At the present time, adrenal medullary insufficiency is just emerging as a recognized syndrome.

In 1959, Broberger, Jungner, and Zetterstrom reported several children with "idiopathic spontaneous hypoglycemia of infancy" (McQuarrie's syndrome) whose epinephrine secretion failed to increase after insulin-induced hypoglycemia. They postulated that the cause of the spontaneous fasting hypoglycemia was a failure of the adrenal medulla to increase secretion of epinephrine during hypoglycemia.

We have studied six infants with this syndrome in whom a failure to increase the urinary excretion of epinephrine with insulin-induced hypoglycemia was also noted. Also of note is the complete absence of the "hypoglycemic symptoms" of palpitations, tachycardia, sweating, and anxiety. These manifestations, unlike the CNS symptoms of lethargy and convulsions, are probably due to increased epinephrine levels rather than to the hypoglycemia per se.

Several adults with a reactive type of hypoglycemia have been studied using the same test. They have had "epinephrine symptoms" during hypoglycemia and a marked increase in epinephrine secretion. An adult with idiopathic adrenal *cortical* insufficiency and another with a bilateral total adrenalectomy (for malignant hypertension) have shown an absence of epinephrine in their urine both before and after insulin-induced hypoglycemia. Also, their symptoms during severe hypoglycemia were limited to the CNS symptom of lethargy.

By determining urinary excretion of epinephrine before and after insulin-induced hypoglycemia it is possible to evaluate the function of the adrenal medulla. This has been shown to be useful in the differential diagnosis of hypoglycemia and it may shed light on the pathologic physiology of other metabolic abnormalities.

Axial Osteomalacia: An Unusual Bone Syndrome. Frame, B., M.D., (Assoc.) Ormond, R. S., M.D.,* Frost, H. M., M.D.,* and Hunter, R. B., M.D.,* Detroit, Mich. (CS)

During the past year, four patients with unique coarsening and sponge-like appearance of the axial skeleton have been observed. Metabolic bone disease, as well as diffuse metas-

tatic malignancy, was considered in the differential diagnosis. Studies of calcium and phosphorus metabolism revealed only minor and inconsistent abnormalities. Bone biopsies in three of the patients who were biopsied demonstrated wide osteoid seams and a marked increase in their number per unit volume, conditions compatible with osteomalacia.

The term axial osteomalacia has been chosen to indicate that the condition appears to be confined to the axial skeleton. It is postulated that the syndrome represents an unusual form of osteomalacia due to a local tissue defect in mineralization of adequately present osteoid tissue.

In the past, osteomalacia has been considered to result from a generalized disturbance of calcium and phosphorus metabolism. As a result of biochemical error, either the serum calcium or the phosphorus, or both, are reduced sufficiently so that proper ionic concentration for deposition of mineral in osteoid tissue is not attained. This older concept of osteomalacia should be expanded to take into consideration factors at the cellular and subcellular level important for the mineralization process.

The four patients with axial osteomalacia will be discussed from the point of view of diagnosis and pathogenesis. An expanded concept and spectrum of osteomalacia will be presented.

Observations on Hypoglycemia Associated with Mesodermal Tumors. Hayes, D. M., M.D.,* Spurr, C. L., M.D., F.A.C.P., Felts, J. H., M.D., (Assoc.), and Miller, E. C., Jr., M.D., (Assoc.), Winston-Salem, N. C. (CS)

The patient presented in this discussion represents the twenty-fourth reported case of the syndrome of spontaneous hypoglycemia associated with tumors of mesodermal origin. In an attempt to clarify the mechanism of hypoglycemia, the rate of utilization of exogenous glucose was determined and efforts were made to modify this rate by the administration of several drugs and hormones. Parallel studies also were done of blood levels of lactic acid, inorganic phosphorus, free fatty acids, and insulin-like activity.

The rate of glucose utilization was found to be normal in this patient (3.38%/min.). This was increased by the addition of insulin (5.53%/min.). The rate of utilization was slowed by the administration of glucagon (2.1%/min.) and corticotrophin (0.86%/min.). Neither L-leucine nor nitrogen mustard perfusion of the abdominal viscera caused any change. Blood levels of lactic acid, determined before and after glucose administration, were found to be within normal limits (6.4 to 17.8 mg./100 ml.). Free fatty acid levels were all noted to be in the high normal range (691 to 1,020 mEq./L.) and did not fluctuate markedly after carbohydrate administration. Circulating inorganic phosphorus was present in normal amounts (2.44 to 3.17 mg./100 ml.) but failed to decrease after carbohydrate. Insulin-like activity in the blood was determined in two laboratories and found to be within normal limits for their respective methods.

As a background for discussion the previously reported cases of this entity are reviewed and pertinent points are tabulated. After considering the possible mechanisms of hypoglycemia it is concluded that two theories have not been explored adequately: (1) the tumor itself demands large amounts of carbohydrate for its own metabolism, and (2) the tumor elaborates an amino acid or similar substance which causes hypoglycemia by a mechanism unlike that of insulin. Hyperinsulinism has not been completely excluded as a cause of this hypoglycemia but seems unlikely on the basis of the present evidence.

Defective Synthesis of Triglycerides from C^{14} Acetate in the Well Controlled Stable Diabetic. Hennes, A. R., M.D.,* Oklahoma City, Okla. (CI)

We have previously reported data in a stable adult diabetic suggesting defective lipid synthesis from 1-C^{14} acetate even when the diabetes is well controlled with insulin.

The present report confirms these findings in studies done with 1-C^{14} acetate in five stable adult diabetics. All were controlled with long-acting insulin and had normal fasting blood sugars and plasma lipid values at the time of the study. All received a diet containing at least 250 gm. of carbohydrate per day and total calories were adjusted so that weight was relatively constant for from five to seven days prior to each study. Patients received 1-C^{14} acetate intravenously in the fasting state and remained fasting for eight hours. Plasma lipid samples were obtained at various intervals during this period and again at 24 hours. Samples were fractionated on silicic acid columns into several classes of lipids.

All diabetics showed marked decrease in incorporation of C^{14} into plasma triglycerides with peak incorporation approximately one-quarter to one-twentieth of that shown by our controls. No diabetic showed increased incorporation of labeled C^{14} into cholesterol. In fact, two of the five showed considerably less synthesis of cholesterol than normal.

In conclusion, we have found no evidence of increased synthesis of plasma cholesterol in the stable adult diabetic; in fact, cholesterol synthesis is sometimes decreased. The de-

fective synthesis of triglyceride from acetate repeatedly demonstrated in the alloxan-diabetic animal also exists in the stable adult diabetic human. In contrast to the alloxan-diabetic animal, however, this defect is apparently not repaired by insulin, even in amounts sufficient to maintain a normal fasting blood sugar.

Effect of Dextro-Isomers of Thyroid Hormones on Serum Cholesterol Levels in Euthyroid Hypercholesterolemic Patients. Hollister, L. E., M.D., F.A.C.P., and Arons, W. L., M. D., (Assoc.), Palo Alto, Calif. (CI)

Both of the naturally-occurring thyroid hormones, l-thyroxine and l-tri-iodothyronine, have been found to lower serum cholesterol levels in euthyroid and hypothyroid hypercholesterolemic subjects. The effects of the dextro-isomers, especially d-tri-iodothyronine, on serum lipids will be presented in this paper. Eleven euthyroid patients with elevated serum cholesterol levels have been treated with d-tri-iodothyronine for one year with doses of from 0.2 to 1.5 mg. per day. The minimal effective dose was 0.2 mg./day, which decreased serum cholesterol by 23% in one patient. Four patients experienced decreases of from 21 to 26% on doses of 0.4 mg. daily. Four patients required doses of from 0.8 to 1.5 mg. to achieve a comparable lowering of serum cholesterol. The remaining two patients have been refractory to doses of less than 1.5 mg., but they have not been treated with this dose long enough to assess effects. None of these patients showed clinical evidence of hypermetabolism with the doses used. Protein-bound iodine tended to rise toward upper limits of normal and the I^{131} uptake was reduced during the treatment period. These metabolic effects will be compared with those previously obtained with l-tri-iodothyronine. A comparison of d-tri-iodothyronine and d-thyroxine in 12 pairs of patients treated for four weeks at each of three dosage levels will also be presented.

Adrenocortical Hyperfunction in Cancer. Kennedy, B. J., M.D., F.A.C.P., Minneapolis, Minn. (CI)

Adrenocortical hyperfunction has occurred in association with carcinomas not originating in the adrenal glands. These cancers included those from the bronchus, thymus, pancreas, and prostate. The syndrome has been characterized by an acute onset, occurrence in young adults, and a short duration of life. The fulminating course appears to be due to the adrenal cortical overactivity.

Three patients have been studied: (1) a 23-year-old female with a small-cell carcinoma of the thyroid with extensive metastases, bilateral pheochromecytoma, and hyperplasia of the adrenal cortex; (2) a 33-year-old male with Hodgkin's disease and adrenal hyperfunction; and (3) a 57-year-old male with metastatic carcinoid and adrenal hyperplasia. Data on these patients and the effect of therapy will be presented.

An effort has been made to explain the occurrence of this syndrome. Diurnal plasma corticoid curves and ACTH stimulation tests have been performed in patients with lung cancer, breast cancer, other cancers, and non-malignant diseases. It appears that in some patients an adrenal cortical hyper-responsiveness exists. The development of metastatic disease may precipitate the fulminating manifestations of adrenal hyperplasia.

Relation of 2-substituted Thiadiazoles to Purine and Nicotinamide Metabolism. Krakoff, I. H., M.D., F.A.C.P., Balis, M. E., Ph.D.,* and Karnofsky, D. A., M.D.,* New York, N. Y. (CI)

2-ethylamino-1,3,4-thiadiazole (TDA) and related 2-substituted thiadiazoles have been found to produce a parallel increase in blood and urinary uric acid in man. Studies of the incorporation into uric acid of isotopically labeled purines and purine precursors have shown that this "uricogenic" effect is the result of an increase in *de novo* biosynthesis of uric acid.

The increase in uric acid synthesis and the characteristic glossitis produced by TDA were blocked by nicotinamide or nicotinic acid and by the nicotinamide precursor, tryptophan. The uricogenic effect, but not the glossitis, was prevented by azaserine (O-diazo-acetyl-L-serine), DON (6-diazo-5-oxo-L-norleucine), and 6-mercaptopurine, compounds which are known to inhibit the biosynthesis of purines or their utilization for nucleic acid synthesis.

The ability of nicotinamide to block the TDA effect has suggested that TDA functions as a "nicotinamide antagonist." However, TDA, which is structurally unlike nicotinamide, has not been found to affect the synthesis of diphosphopyridine nucleotide (DPN), the principal nicotinamide-containing co-enzyme, nor does it produce the clinical features of pellagra, a disease of nicotinamide deficiency. 6-amino-nicotinamide, a structural analog of nicotinamide, does produce toxicity which clinically resembles pellagra, it does inhibit DPN

formation and yet, like nicotinamide, it is able, in animal systems, to block the effects of TDA.

It is suggested that different "nicotinamide antagonists" may act by different mechanisms or at different metabolic sites and that potent antimetabolites may function as metabolites in opposing the action of a different type of anti-metabolite. Further studies are necessary to clarify these interrelations and the relation of nicotinamide metabolism to purine biosynthesis.

Studies on Experimental Alcaptonuria and Ochronosis. La Du, B. N., Jr., M.D.,* O'Brien, W. M., M.D.,* and Zannoni, V. G., M.D.,* Bethesda, Md. (CI)

A specific enzymatic method for the determination of homogentisic acid in blood, urine, and tissues has recently been developed in our laboratory. The method has been utilized to study the tissue distribution of homogentisic acid after its intraperitoneal administration to guinea pigs and to study the factors which facilitate the removal of homogentisic acid from the tissues. Within 30 minutes after administration of homogentisic acid, relatively high concentrations were found in skin and cartilage; much lower concentrations were present in liver, muscle, and brain. No significant differences in the distribution were observed in young versus adult animals. The unusual distribution pattern is in agreement with the presence of ochronotic pigment in the connective tissues of older alcaptonuric subjects.

The concentration of homogentisic acid in the tissues rapidly falls because of two factors: (1) rapid metabolism by homogentisic acid oxidase in liver and kidney, and (2) renal secretion of the acid. Even though they lack homogentisic acid oxidase, alcaptonuric subjects can still secrete the acid, and no doubt this accounts for the many years required for the development of ochronesis and ochronotic arthritis. A study of the secretory activity in alcaptonuric individuals has been made after the oral administration of homogentisic acid. Most of the administered dose is rapidly secreted in the urine and the plasma concentration returns to the base value within two or three hours. Further studies are being made on the renal secretion of homogentisic acid in guinea pigs. The inhibitory effect of some agents on this activity is being investigated.

Inheritance of Defective Organification of Iodine in Familial Goitrous Children. Parker, R. H., M.D., (Assoc.), and Beierwaltes, W. H., M.D., F.A.C.P., Ann Arbor, Mich. (CI)

Defective organification of iodine has been studied in goitrous cretins and their siblings. We wish to report a genealogy of 90 members of four generations with two related sibships in which seven of 11 children in the one and two of seven children in the other were cretins. Rapid thyroidal uptake and early release of I^{131}, prompt and marked discharge of I^{131} after KSCN, and the finding of iodide alone on serum and urine chromatography up to 48 hours after 400 μc. of I^{131} constitute evidence for a defect in thyroidal organification of iodine in these cretins. Five apparently normal siblings and eight other relatives failed to show laboratory evidence of this defect. This relationship allows us to make a statement on the mode of inheritance of the biochemical defect associated with this type of cretinism. However, the incidence of goiter in the family, in particular in the mothers of the cretins, suggests a minor defect in the heterozygous state undetectable by our methods, so that although the mode of inheritance is recessive, there remains a question as to whether or not it can be defined as completely recessive. Due to ideal treatment in the smaller sibship, the expression of the genotype was completely suppressed. This is in contrast to the situation in the larger sibship, in whom treatment was virtually omitted and whose course illustrates the natural history of this disease at various age levels.

Stimulation of Glucose Oxidation in Thyroid by Thyroid Stimulating Hormone (TSH) and Other Substances. Pastan, I., M.D.,* and Field, J. B., M.D.,* Bethesda, Md. (CI)

Although TSH has been shown to increase thyroid growth, respiration, iodine, and phospholipid metabolism, its mechanism of action is unknown. We noted that the oxidation of glucose-1-C^{14} and glucose-6-C^{14} to $C^{14}O_2$ by thyroid slices in vitro was stimulated five minutes after the addition of TSH. This early effect suggested that TSH acts directly on glucose oxidation or a closely related metabolic step, and that previously noted effects of TSH were secondary. This stimulation of glucose oxidation was specific since: (1) TSH had no effect on the glucose oxidation of many other tissues; (2) none of the other

anterior pituitary hormones affected the thyroid; (3) as little as 0.1 mU. of a highly purified TSH preparation was effective. Although glucose uptake from the media was also stimulated by TSH, this did not seem to be the mechanism of the increased glucose oxidation, since insulin, which is thought to act on glucose transport, also stimulated glucose uptake. It had no effect on the oxidation of glucose to CO_2.

Low concentrations of acetylcholine (10^{-8} M) also increased glucose oxidation and glucose uptake by thyroid. However TSH did not appear to act through acetylcholine as an intermediary, since atropine inhibited the increase caused by acetylcholine but did not inhibit that produced by TSH. Epinephrine, norepinephine, and serotonin, which are known to affect thyroidal iodine metabolism, also stimulated the oxidation of glucose-1-C^{14} to $C^{14}O_2$.

The possible mechanism of action of TSH on glucose oxidation and the implications of this effect in the overall physiology of the thyroid gland will be discussed.

Hypothalamic Regulation of Thyrotrophic and Somatotrophic Hormone Secretion. Reichlin, S., M.D.,* St. Louis, Mo. (CI)

Among other endocrine abnormalities that follow hypothalamic destruction in the rat, lesions in specific areas lead to a depression of thyroid function and to impaired growth.

Anterior lesions cause low thyroidal I^{131} uptake, I^{131} release rate, and plasma PBI; normal responses to increased and decreased blood levels of thyroid hormone are maintained, however. This finding is interpreted to mean that the pituitary is autonomously responsive to thyroxine concentration but that its level of reactivity is "set" by a hypothalamic mechanism acting via the pituitary stalk. Since the "thyrotrophic area" was shown to be anatomically close to the temperature regulating area, it is likely that the anterior hypothalamus contains centers for the integration of short-term autonomic and long-term metabolic heat regulating mechanisms.

Massive anterior-ventral lesions reduce linear and bone growth rate from one-third to one-half the normal, even when food intake is controlled by pair feeding. Appropriate treatment of known lesion-induced hormone deficiencies (thyroxine, testosterone, vasopressin) does not restore growth to normal. That impaired growth is due to specific growth hormone (GH) deficiency is further suggested by the fact that anterior pituitary content of GH is reduced to about 15% of normal (tibial epiphysial width assay). The lesions and the pertinent hypophysial anatomy will be demonstrated.

Motor Nerve Conduction Velocity in Diabetes Mellitus. Skillman, T. J., M.D.,* Johnson, E. W., M.D.,* Hamwi, G. J., M.D., F.A.C.P., and Driskill, H. J., M.D.,* Columbus, O. (CI)

Disturbances in neurologic function occur in from 25 to 90% of diabetic patients. Although neurologic deficits are largely considered to be afferent, motor nerve involvement occurs frequently. Function of the motor unit may be measured in a precise quantitative manner with modern instruments: The method consists of percutaneous stimulation of the ulnar and peroneal nerves at two points along their course. Electrical potential from the induced contraction is then picked up over the abductor digiti quinti and extensor digitorum brevis. Latency of response is photographed from an oscilloscope. Nerve length between stimulation points is measured on the skin. Conduction velocity is determined by dividing the distance between stimulation points by the duration of latency of response. Temperature corrections are made by measuring muscle temperature directly with a needle thermistor. Normal values are 49.3 ± 5.7 meters/sec. (M/S) for the peroneal nerve and 56.4 ± 6.3 M/S for the ulnar nerve. Studies were made in 103 diabetics who averaged 52 years of age and 8 years' duration of diabetes. Seventy-three of these subjects were shown to have one or more objective signs of peripheral neuropathy and their peroneal nerve conduction was found to be 36.5 ± 5.1 M/S compared to that of 43.6 ± 6.0 M/S in the 30 patients without clinical neuropathy ($P < 0.01$). Similar reductions were found with respect to ulnar conduction velocity. Reduced velocity generally correlated with severity of clinical neuropathy and with severity of complications such as retinopathy and nephropathy. Tangential studies employing conduction velocity as an index to the response to treatment of peripheral neuropathy have also been made, and suggest that measurement of conduction velocity is useful for these evaluations.

Peptic Ulcer Disease in Hyperparathyroidism: An Analysis of Fifty-two Cases. Wilder, W. T., M.D.,* Frame, B., M.D., (Assoc.), and Haubrich, W. S., M.D. (Assoc.), Detroit, Mich. (CS)

There has recently been increased interest in the clinical relationship between peptic ulcer and hyperparathyroidism. The importance of this association is demonstrated by the

fact that seven of the last nine patients with hyperparathyroidism seen at the Henry Ford Hospital have had peptic ulcer. An increased awareness of this association has led to an overall increased incidence of hyperparathyroidism being diagnosed at this hospital. In our experience, the presence of peptic ulcer has been even more important than kidney stones in the diagnosis of parathyroid hyperfunction. In three patients, symptoms of peptic ulcer disease were the only clue to the diagnosis of hyperparathyroidism.

An analytical review of 52 cases of peptic ulcer disease in hyperparathyroidism gathered from the files of Henry Ford Hospital and the literature will be presented. The following conclusions were reached: (1) There is a relative increased incidence in females when peptic ulcer is associated with hyperparathyroidism; (2) Gastric and jejunal ulceration possibly has more significance than duodenal ulceration in hyperparathyroidism; (3) Peptic ulcer disease over ten years' duration occurred in 23 of the 52 patients reviewed. A duration of less then five years has been reported with increased frequency in the last several years since this relationship has been stressed; (4) In 23 of 37 cases of hyperparathyroidism (in which information was sufficient for analysis), peptic ulcer was the earliest single symptom complex that could, retrospectively, be attributed to hyperparathyroidism; (5) The majority of patients showed evidence of unusually severe peptic ulcer disease; (6) In those cases where sufficient follow-up studies were available, 30 of 33 cases demonstrated improvement in ulcer symptoms after removal of parathyroid adenoma.

A discussion of the present status of clinical and experimental studies pertaining to the relationship of these two diseases will be given.

GASTROENTEROLOGY

Comparative Usefulness of Qualitative and Quantitative Stool Occult Blood Tests in the Diagnosis of Gastrointestinal Disease. Ebaugh, F. G., Jr., M.D., F.A.C.P., and Beeken, W., M.D.,* Hanover, N. H. (CS)

Previous work in this laboratory has shown by a chemical photospectrometric technic that the normal 24-hr. fecal blood loss is 1.70 ± 1.2 ml., and is not influenced by diet or iron therapy. Utilizing this chemical quantitative test, it was found that the *qualitative* benzidine-2HCL test on three serial stool samples gives 50% false positive and 2% false negative results. Less than 6% of false positive *qualitative* tests are caused by concentration of the 24-hr. stool volume or by unequal distribution of blood in the stool. Fifty per cent of patients with gastrointestinal malignancies show normal 24-hr. *quantitative* fecal blood loss. Eighty per cent of patients with cancer and 16% with peptic ulcer, having increased fecal blood loss, failed to achieve normal values in three successive 24-hr. specimens after medical therapy. None of 22 patients on Dicumarol therapy showed increased fecal blood loss. Illustrative cases will be presented in whom up to 300 ml. of fecal blood was lost per day without occurrence of melena or symptoms leading the physician to suspect gastrointestinal blood loss. It is concluded that the quantitation of fecal blood loss is a valuable adjuvant in the diagnosis of gastrointestinal cancer and peptic ulcer, particularly in patients with initial negative x-ray studies.

Observations on Steatorrhea Associated with Gastric Hypersecretion and Pancreatic Islet Cell Neoplasm. Haubrich, W. S., M.D., (Assoc.), O'Neil, F. S., M.D.,* and Block, M. A., M.D.,* Detroit, Mich. (CS)

Of the reported cases of pancreatic islet cell tumor associated with gastric hypersecretion (Zollinger-Ellison syndrome), about one-third mention diarrhea as a prominent symptom. A history of diarrhea was elicited in all four patients exhibiting this syndrome at The Henry Ford Hospital within the past three years. One of these patients, who had neither symptoms nor signs of peptic ulcer disease, sought medical care primarily because of frank steatorrhea, weight loss, and progressive weakness. This patient provided an opportunity for the clinical and laboratory investigation of steatorrhea in this syndrome and its response to treatment.

Stomach aspiration yielded a prodigious volume of gastric secretions (6.9 liters in one 12-hour overnight period) with a high acid content (over 100 mEq./L. of free HCl). An initial fat balance study demonstrated steatorrhea (fecal fat equivalent to 26% of ingested fat). Unexpectedly, fecal fat excretion was reduced to 15.6% with a low-gluten diet. Sustained stomach aspiration induced a profound hypochloremic alkalosis but was also attended by a total absence of stools for seven days. When all gastric secretions were aspirated but returned to the duodenum after the neutralization of acid, the fecal fat excretion was only 6.2%. The diagnosis was confirmed by finding metastatic islet cell neoplasm in a parapancreatic lymph node, and a clinical remission has followed subtotal gastrectomy.

It is postulated that a major factor in the steatorrhea was the inactivation by voluminous, strongly acid gastric juice of the digestive enzymes in the proximal intestine.

Newer Concepts of Whipple's Disease. Holt, P. R., M.D.,* Cohen, A. S., M.D.,* and Isselbacher, K. J., M.D.,* Boston, Mass. (CS)

Whipple's disease was described and originally considered as an intestinal lipodystrophy. Peroral jejunal biopsy and early exploratory laparatomy have led to a more frequent diagnosis during life, and it has become apparent that the disease is systemic with pathologic involvement of lymph nodes, heart, lungs, and other organs. These tissues show a characteristic infiltration by macrophages filled with periodic acid-Schiff staining inclusions which have now been studied in the electron microscope and which reveal a very striking appearance associated with dense virus-like particles. The significance of these findings will be discussed.

It is of importance that while malabsorption is a feature of this disorder, the light and electron microscopy of the intestinal mucosa reveal changes completely different from idiopathic steatorrhea. Whipple's disease was previously believed to be uniformly fatal, but vigorous treatment with steroids and occasionally with antibiotics has been shown to induce prolonged remissions. In one well-documented case to be reported, followed for nine years, all clinical manifestations and morphologic changes of the disease have completely disappeared.

The presentation will include a review of current concepts based on our clinical observations and basic studies of five patients, as well as a review of over 100 additional cases.

The Mechanics of Malabsorption. Ingelfinger, F. J., M.D., F.A.C.P., Boston, Mass. (ML)

Normal absorption depends initially on active digestion, and eventually on the presence of healthy mucosal cells. As an intermediate requirement, however, an adequate contact must be established between the products of digestion on the one hand, and a sufficient number of healthy and specifically endowed absorbing cells, on the other. When this contact is inadequate, absorption may suffer in proportion. Mechanisms responsible for preventing adequate contact may act singly or in combination:

1. The area of absorbing surface is curtailed by ablation, by by-pass, or by a degenerative loss of villous projections. The effects of such curtailment are determined not only on the basis of length of intestine involved, but also by quantitative and qualitative differences existing between jejunal and ileal mucosae. In terms of absorbing area, the jejunum is 20 times as "long" as the ileum; yet the contribution of the ileum to normal absorption may be crucial for certain substances.

2. The period of contact between the products of digestion and the absorbing surface is curtailed by motor disorders or certain by-pass arrangements. Although the motor disorder usually incriminated is an excessively rapid transit, subtle influences on absorption may also be exerted by the pattern of distribution of time in the small bowel, the intensity of mixing activity, and the time of contact permitted in various parts of the intestine as related to qualitative differences in the mechanisms responsible for the absorption of different substances.

The products of digestion are diverted to other pathways. Abnormal bacterial populations may consume, alter, or by other means make nutrients unavailable for absorption. Unabsorbed materials in intestinal chyme may, in turn, interfere with absorption of other substances either by solvent affinities or by biochemical action.

These mechanisms play a variable but important role in various clinical syndromes of malabsorption.

Observations on Secondary Malabsorption Syndromes of Intestinal Origin. Scudamore, H. H., M.D., F.A.C.P., Rochester, Minn. (CS)

A malabsorption syndrome may develop in the presence of several different diseases or conditions in which absorption from the small intestine is impaired. A classification of these conditions is presented, with a consideration of the pathophysiologic factors leading to impaired absorption. Special emphasis is given to the malabsorption syndrome that may be associated with the following disease states: regional enteritis, amyloidosis, actinic enteritis, scleroderma, Whipple's disease, lymphomas, internal fistulas, and diverticulosis. The clinical manifestations of each of these syndromes are discussed and exemplified with illustrative cases. The differential diagnosis between nontropical sprue and related conditions is considered. The importance of jejunal biopsy and abdominal exploration in diagnosis is emphasized. Finally, treatment and prognosis in these various conditions are

outlined. These secondary malabsorption syndromes are clinically interesting and significant diseases which are not commonly encountered.

Effect of Portacaval Shunt on Hypersplenism. Tumen, H. J., M.D., F.A.C.P., and Sullivan, B. H., Jr., M.D., F.A.C.P., Philadelphia, Pa. (CS)

Patients with cirrhosis may have a variety of hematologic disturbances. Some of these—anemia, neutropenia, and thrombocytopenia—are attributed to hypersplenism. This is secondary to portal hypertension, which may also lead to the formation of esophageal varices. It is important to determine whether the hematologic consequences of hypersplenism decrease following shunt procedures that lower portal pressure, and also to learn whether, when hypersplenism is marked, splenectomy is required in addition to a shunt operation.

A study was made of the effect of end-to-side portacaval shunt upon the anemia, neutropenia, and thrombocytopenia of 25 patients with cirrhosis who required portal decompression because of esophageal varices. It was found that the anemia was not always corrected simply by portacaval shunt, probably because of the continuing effect of other causes of anemia in cirrhosis. Neutropenia tended to disappear gradually following shunting and the platelet count generally rose. These changes seemed to follow lowering of the portal hypertension and decrease in splenic size. In general, therefore, portacaval shunt sufficed to correct the hypersplenism of portal hypertension, and splenectomy was unnecessary. Rarely, however, with thrombosis of a shunt or progressive liver disease marked thrombocytopenia developed and, in these circumstances, secondary splenectomy became necessary.

The Physiology of Heartburn. Tuttle, S. G., M.D., (Assoc.), Rufin, F., M.D.,* and Grossman, M. I., M.D.,* Los Angeles, Calif. (CS)

Twelve patients with endoscopic evidence of esophagitis and with complaints of heartburn were studied during symptomatic episodes, by simultaneous measurement of respiration and intraluminal pressures and pH. After 300 ml. of HCl were placed in the stomach to insure the presence of gastric acidity, a small pH electrode and four water-filled polyvinyl catheters, spaced 5 cm. apart, were passed through the nares into the stomach and a baseline recording was made. The sensing device was then withdrawn into the esophagus to a level such that the bulb of the glass electrode was 5 cm. above the effective diaphragmatic hiatus. The patient was given a signal marker which he depressed when he experienced symptoms. Analysis of the records obtained showed that: 1. heartburn was associated with a fall in pH below four; 2. symptoms disappeared when the pH rose above this level; 3. there were no changes in the intraluminal pressures that could be correlated with pH; and 4. mean esophageal pressure (measured as a difference from mean fundic pressure) was not different from values seen in individuals without reflux.

In eight patients with symptomatic esophagitis, air was introduced into the stomach to induce belching. For 10 seconds prior to gaseous eructation, there was simultaneous elevation of intraesophageal pressure. Expulsion of air per os was then followed by a progressive esophageal peristaltic wave. A fall in pH was noted in only three patients. During each episode, the subject complained of heartburn duplicating his spontaneous complaints.

It thus appears that heartburn may occur spontaneously with gastroesophageal regurgitation without esophageal motor changes, and in association with belching and an altered motility pattern in the absence of detectable reflux.

Hematology

Proteolysis, Fibrinolysis and Coagulation: Significance in Thrombolytic Therapy. Alexander, B., M.D.,* and Pechet, L., M.D.,* Boston, Mass., and Kliman, A., M.D.,* Bethesda, Md. (ML)

Now that infectious nutritional neonatal and other diseases are controllable, thromboembolic disease has become a major threat to life and limb. Expanding knowledge of the blood fibrinolytic system and its potential therapeutic use have stimulated renewed interest in blood proteases, particularly in relation to coagulation. Additional significance derives from their possible etiologic importance in atherosclerosis, according to the Rokitansky-Duguid-Astrup concept of imbalance between arterial wall fibrin deposition and failure of its removal.

Our investigations to be presented demonstrate:

1. A combination of *in vivo* coagulation experimentally induced by the generalized Shwartzman reaction, with streptokinase (SK) activated plasminogen (fibrinolysin), produces profound clotting defects (afibrinogenemia and poor thromboplastin generation) and severe hemostatic failure, in contrast to the relative innocuousness of either alone.

2. Similarly, fibrinolysin *in vitro* causes prompt inhibition of the thrombin-fibrinogen interaction. This, plus a minute amount of thrombin, has an even more profound effect in rendering the fibrinogen no longer clottable, thus completely simulating the *in vivo* "afibrinogenemia." These observations are pertinent to thrombolytic therapy for conditions where intravascular coagulation may be occurring.

3. The same clotting abnormality is produced by trypsin.

4. Further data indicate that plasmin, thrombin, and trypsin act competitively on fibrinogen. Whichever of these proteases reaches this substrate first will block the action of the others.

5. Other protease studies will be presented. *In vitro* trypsin and papain markedly activate clotting Factors II (prothrombin), VII (proconvertin) and X (Stuart), resembling the action of thromboplastin. Plasmin and thrombin are contrastingly inert, whereas they can first activate and then rapidly destroy Factor V (Ac-globulin). This explains its depression observed in thrombolytic therapy.

Thus, blood tryptases and trypsin may trigger intravascular coagulation rather than combat it. The use of trypsin for thrombolysis is therefore deplored. The findings also draw attention to the tryptase-antitrypsin system in normal blood, and its possible imbalance in producing thrombotic disease.

All of these observations help to elucidate some clinical and clinicolaboratory findings in acquired "afibrinogenemia" (pancreatic, prostatic, and other malignancies, anoxia, shock, sepsis, defibrination syndromes of pregnancy, surgical pulmonary manipulation, etc.), and induced (therapeutic) "fibrinolytic" states.

Lupus Erythematosus and the Antigens of the Nucleus. Atchley, W. A., M.D., (Assoc.), San Francisco, Calif. (CI)

The serum of patients with systemic lupus erythematosus (SLE) frequently contains antibodies which react with the isolated nucleus, fractions of the nucleus, and, less consistently, various components of the cytoplasm. This suggests but does not prove that SLE may be a disease of auto-immunity.

This laboratory has developed a new and fruitful method of studying the interaction between SLE serum and biochemical fractions of the cell, with particular emphasis on material derived from the nucleus. Leukocytes obtained from patients with leukemia are washed thoroughly and extracted in dilute glycine. The extract is extremely rich in deoxyribonucleic acid (DNA) and associated proteins (P). The DNA-P has a typical ultraviolet spectrum and a characteristic insolubility in physiologic saline. When injected into rabbits it is antigenic and gives rise to a well-defined precipitin line in agar.

The DNA-P can be separated from the other components of the extract by electrophoresis on cellulose acetate membranes, and appropriate histochemical staining of the membranes shows that all the DNA migrates rapidly in a single homogeneous band to which is complexed the bulk of the histone of the cell. In some instances, a second less-well-defined band of histone is seen, which migrates more slowly.

After electrophoretic separation of the nuclear material, SLE serum can be added to the membrane and allowed to develop precipitin lines in the process of immunoelectrophoresis. In this way, SLE serum has been shown frequently to contain antibodies to the DNA-histone complex and, less frequently, antibodies to another major component of the extracts, which is probably the histone not attached to the DNA.

This approach is a means of gaining insight into the serologic individuality of patients with SLE, and, by using SLE serum as a reagent, it is a means of defining the antigenic composition of the cellular nucleus.

Organ and Bone Marrow Transplants. Ferrebee, J. W., M.D.,* Cooperstown, N. Y. (ML)

Transplants of bone marrow have been found to restore hematopoiesis in animals rendered aplastic by lethal exposure to radiation. Animals so restored have been found to accept transplants of other tissue from their marrow donors. Efforts to expand this information to the point of clinical usefulness in either the treatment of radiation casualty or the transplantation of whole organs have revealed certain problems. Clearly immunologic tolerance can be acquired. The difficulty has been to make the methods of its acquisition

clinically acceptable. Investigation has revealed several methods of promise: the use of fetal rather than adult hematopoietic tissue to restore hematopoietic and lymphopoietic functions in the treated host; the use of fractional sublethal radiation or chemotherapy, primarily antimetabolites, to control the reciprocal reactions of host and graft. Examples will be given and the current status of the field will be reviewed briefly.

Coagulation Defects—Bleeding Tendencies. Lewis, J. H., M.D.,* Pittsburg, Pa. (ML)

1. Normal hemostatic mechanisms.
2. Classification of hemorrhagic diseases, both primary and secondary.
3. Differential diagnostic methods.
4. Research approaches to the problems of blood coagulation and hemostasis.

The John Phillips Memorial Lecture: The Diagnosis of Common Hereditary Hemorrhagic Diseases. Quick, A. J., M.D.,* Milwaukee, Wis. (CS)

The diagnostic triad—history, physical, and laboratory—is the key to the study of the hereditary bleeding diseases. From the history, it can usually be determined whether the bleeding is spontaneous (capillary) or traumatic (arteriolar). The prototype of the first is found in thrombocytopenia while the second is characteristic of hemophilia.

The three hereditary types and the hemorrhagic diseases belonging to them are: 1. sex-linked recessive- classical hemophilia and hemophilia B (also known as Christmas disease and PTC deficiency); 2. autosomal dominant-telangiectasia and von Willebrand's disease (pseudohemophilia); and 3. autosomal recessive- hypoprothrombinemia vera, afibrinogenemia, hyperheparinemia, and deficiencies of factors V (labile factor), VII (stable factor), and X (Stuart-Prower).

Careful inspection of the skin in the physical examination is important. The superficial ecchymoses are typical of spontaneous capillary bleeding, whereas the deeper hematoma of the traumatic type occurs in hemophilia. Telangiectasia is diagnosed solely by the typical skin and mucous membrane lesions. Joint bleeding is always of the traumatic type.

The definitive diagnosis of a bleeding disease usually is established by laboratory tests. The clotting and bleeding times and the tourniquet test are useful but not specific. The key diagnostic tests are the prothrombin time and the prothrombin consumption time. With the first test, deficiencies of the prothrombin complex (prothrombin, factors V, VII, and X) can be detected, and by minor alteration of the procedure, each can be quantitatively estimated. The prothrombin consumption test is an indirect measure of the generation of intrinsic thromboplastin. Low results are obtained in thrombocytopenia, hemophilia, hemophilia B, and several other diseases. By means of simple additional steps and modifications of the basic test, various factors participating in the generation of thromboplastin can be quantitatively determined.

The Current Status of the Macrocytic Anemias. Vilter, R. W., M.D., F.A.C.P., Cincinnati, O. (ML)

Macrocytic megaloblastic anemias occur because of single or combined deficiencies of folic acid, vitamin B_{12}, or ascorbic acid. Many other situations can result in mild or moderate macrocytosis, such as chronic liver disease, hemolytic anemia, refractory anemia (chronic bone marrow failure), but none of these produce a true megaloblastic bone marrow picture.

Chemical, microbiologic, and isotopic studies of patients with macrocytic megaloblastic anemia indicate that several deficiencies usually are responsible. Even the patient with a Shilling test typical of pernicious anemia, which is due to vitamin B_{12} deficiency, often is deficient in folic acid and has a very low ascorbic acid level as well. Other vitamin B_{12} deficiency states may occur in the postgastrectomy patient, the true vegetarian, the patient harboring the fish tape worm, or may be combined with folic acid deficiency in nutritional macrocytic anemia, and sprue. Folic acid deficiency usually accounts for the megaloblastic anemia of pregnancy and cirrhosis, though in these cases, too, there may be lack of vitamin B_{12} as a result of poor diet. In scurvy and in infancy, megaloblastic anemia may occur because of combined deficiencies of folic and ascorbic acid.

Experimental evidence points to folic acid metabolism as the key to the megaloblastic anemia problem. Vitamin B_{12} and ascorbic acid deficiencies interfere with effective formation of the folic acid coenzymes, and a deficiency of these substances appears to be the primary cause of the megaloblastic maturation arrest. These interrelationships will be discussed.

Infectious Diseases and Immunology

Fungistatic Effects of Cell-Free Human Serum. Baum, G. L., M.D., F.A.C.P., and Artis, D., B.S.,* Cincinnati, O. (CI)

Previous work has shown that cell-free human serum is bacteriostatic and in some instances bactericidal. This has been a nonspecific effect and not related to previous immunization. The present study was done with several species of pathogenic fungi and with species that are only occasionally pathogenic for humans.

Cryptococcus neoformans, Sporotrichum schenckii, Candida albicans, Penicillium species and *Aspergillus* species were tested for inhibition by cell-free human serum obtained by the usual method of venipuncture and frozen until the experiments were set up. Physicians and patients were sources of serum. Both individual and pooled sources were used.

Culture tubes were filled with a mixture of 2.25 ml. Sabouraud's broth and 2.25 ml. human serum. To the first of each set of eight such tubes a heavy concentration of one of the first three fungi mentioned above was added. This was then diluted through the remaining seven tubes so that concentrations of yeast cells from 5,000,000 to 5 per ml. were set up. After incubation of the tubes for 10 days, pour plates were made with Sabouraud's agar and the growth of the fungi was observed. Definite inhibition of all organisms was noted. Growth of all organisms from control tubes of broth alone was heavy on the pour plates. No inhibition of the *Penicillium* and *Aspergillus* species set up in similar systems was noted.

Immunologic implications of these experiments are discussed, emphasizing the ubiquitous nature of the fungi involved and the infrequency of active human infection.

Studies of Viral Respiratory Disease in Marine Personnel. Bloom, H. H., Ph.D.,* Camp Lejeune, N. C., Johnson, K. M., M.D.,* Bethesda, Md., Mufson, M. A., M.D., Camp Lejeune, N. C., Jacobsen, R., M.D.,* Brookline, Mass., and Chanock, R. H., M.D.,* Bethesda, Md. (CS)

Although major advances have been made in the unravelling of a significant portion of viral respiratory disease in children, little is definitively known concerning adult mankind's most common disorder—the cold.

Intensive study of respiratory disease produced by adenoviruses in young men during the recruit phase of military training has been highly rewarding, but only for that special group. Recent discoveries have provided the virologist with an almost bewildering host of potential new cold viruses.

A study of such illnesses in nonrecruit military personnel suggests that different agents are prevalent at different times and produce essentially similar mild illnesses in distinct patterns. Spill-over of adenovirus infection from recruits to more seasoned men has been observed, usually in the winter months. A generalized outbreak of infection by Coe virus (Coxsackie A-21) occurred in the fall of 1960. Observed disease was mild and exclusively respiratory, in distinction to that seen with certain other enterovirus infections. Finally, certain agents, including the para-influenza and respiratory syncytial viruses, commonly found in association with more severe pediatric illness, were recovered from adults with mild upper tract symptoms. More than 4,000 individuals have been included in the study to date. Analysis of these cases indicated that several simple procedures facilitated recovery of different viruses. These included inoculation of fresh unfrozen specimens into at least two types of tissue cultures, use of a rotating drum for incubation of cultures, and the sampling of patients within 48 hours after onset of respiratory symptoms.

This report will highlight these findings, outline the varied epidemiologic patterns they suggest, and briefly consider the prospects for eventual control of viral respiratory disease.

A Clinical and Serologic Study of the Latex Fixation Test in Leprosy. Cathcart, E. S., M.D.,* and Williams, R. C., Jr., M.D.,* Boston, Mass., Ross, H., B.S.,* Carville, La., and Calkins, E., M.D.,* Boston, Mass. (CS)

While studying the latex fixation test in patients with nonrheumatic diseases, positive reactions were noted in a large proportion of leprosy sera. A study was therefore designed to determine the clinical and serologic significance of this observation. One hundred and one patients with leprosy, chosen at random, in the USPHS Hospital, Carville, were interviewed and examined personally by us. Data were obtained about each patient concerning his past and present medical history, physical examination, laboratory findings, joint x-rays, and special serologic tests.

Many of the patients were found to have chronic diseases other than leprosy, especially syphilis, diabetes, tuberculosis, and malaria. Only three subjects had rheumatoid arthritis. The incidence of secondary amyloidosis, proved by gingival biopsy and Congo red tests, was unexpectedly high (24%). Using heat inactivated leprosy sera, 24 positive latex fraction reactions and 15 positive sheep cell agglutination tests were obtained. In an additional 20 patients the latex fixation test was positive using a euglobulin fraction. Adsorption experiments with lepromin and tuberculin, precipitin reaction with aggregated gamma globulin, and diffusion on agar gel provided evidence that the agglutination factors in leprosy sera are similar to the so-called rheumatoid factors.

Duration, type of course, and severity of disease appeared to be unrelated to the presence of positive serologic tests. The incidence of the other diseases associated with leprosy and their relationship to the latex fixation and sheep cell agglutination tests will be discussed.

Disseminated Coccidioidomycosis: Its Natural Course and Treatment. Colwell, J. A., M.D.,* Chicago, Ill., and Tillman, S. P., M.D.,* Atlanta, Ga. (CS)

With the development of effective antifungal chemotherapy, early and accurate diagnosis of disseminated coccidioidomycosis is imperative. In the present study, 50 cases of coccidioidomycosis were first observed shortly after the onset of the disease and were followed for up to three years. The clinical course in 42 patients with primary pulmonary coccidioidomycosis was compared with that of eight patients with disseminated coccidioidomycosis. It was found that certain characteristics clearly separated the two groups. Soon after the primary infection, dissemination (extrapulmonary spread) could be first suspected in those patients with a history of weight loss, prolonged duration of generalized symptoms (malaise, syncope), and chest roentgenograms showing paratracheal adenopathy. Four weeks after the initial infection, a presumptive diagnosis of disseminated coccidioidomycosis could be made on the bases of persistent temperature elevation, physical evidence of extrapulmonary spread (adenopathy, skin lesions, meningeal signs), and unstable chest roentgenograms. Extrapulmonary spread occurred within seven weeks of the primary infection in seven patients and was first recognized in the twentieth week in the other.

Amphotericin B was an effective agent in the therapy of disseminated coccidioidomycosis. Five patients received a total intravenous dosage of from 1.15 to 6.39 gm. for from five to 41 weeks. All had a fall in coccidioidal complement fixation titers and disappearance of physical and roentgenologic evidence of disease. No evidence of exacerbation was seen from 17 to 64 weeks after infusions were stopped. Two patients with lymphogenous spread, recognized and treated early in the course of the disease, required the least medication (1.15 to 1.83 gm. for 16 and 18 weeks). Two others with early lymphogenous spread were treated late in the course of dissemination and required larger doses (2.1 to 5.09 gm. for five and 41 weeks). Skin lesions cleared slowly. Response in one patient with lymphogenous dissemination was clearly better than in an untreated control. Reversible renal abnormalities were the major toxic side effects of therapy with amphotericin B.

The conclusions of this study are: (1) Extrapulmonary spread of coccidioidomycosis can be accurately predicted by clinical means within one month of the initial infection, and (2) Amphotericin B is an effective agent in the therapy of disseminated coccidioidomycosis, particularly when it is given early in the course of this disease.

Observations on the Role of Serotonin in Shock due to Bacterial Endotoxin. Davis, R. B., M.D.,* and Meeker, W. R., M.D.,* Minneapolis, Minn. (CI)

The possible role of serotonin in the trigger mechanism producing shock due to bacterial endotoxin has been investigated. Prior studies in our laboratory showed that profound alterations occurred in serotonin concentrations within 15 sec. after the injection of *Escherichia coli* endotoxin, coincident with significant hemodynamic changes and marked intravascular agglutination of platelets in the dog. Actual release of serotonin, however, was not conclusively demonstrated.

After lethal amounts of endotoxin were injected in rabbits, the in vivo liberation of serotonin clearly was demonstrated in carotid artery blood. A statistically significant elevation of plasma serotonin was demonstrated after endotoxin, with serum and platelet alterations closely resembling those in the dog. In vitro experiments undertaken to show serotonin liberation revealed platelet clumping, a significant fall in the number of platelets, and liberation of serotonin in siliconed glassware, after endotoxin incubation.

Serotonin injection in the dog, done in order to determine the hemodynamic significance of serotonin liberation, showed profound alterations in arterial pressure after serotonin. When serotonin or histamine (previously shown by others to be released after endotoxin)

alone was injected, the initial pressure changes seen after endotoxin were not reproduced. Both, however, when injected in proper sequence in the sites of proved release, almost exactly simulated the initial pressure changes of endotoxin. Using inbred mice, significant mortality reduction was obtained with mono-amine oxidase inhibitors given before endotoxin, suggesting a role of serotonin in the lethal response to endotoxin as well.

These studies clearly demonstrate that serotonin release is effected by endotoxin, and suggest that release of this vasopressor agent plays a role in the development of shock due to *Esch. coli* endotoxin.

The Specific Serum Antimycobacterial Activity Test as a Guide to the Appropriate and Adequate Chemotherapy of Pulmonary Tuberculosis. Gill, R., M.D.,* Kass, I., M.D., F.A.C.P., Russell, W. F., Jr., M.D.,* and Dye, W. E., Ph.D.,* Denver, Colo. (CI)

Serum microbiologic or chemical assay studies performed at National Jewish Hospital on antimicrobial agents such as streptomycin, isoniazid, cycloserine, pyrazinamide, and kanamycin, have clearly shown that patients achieve different serum concentrations of these antimicrobial agents even when dosages are adjusted according to body weight. Likewise, routine susceptibility studies have proved to be of value in determining the choice of the antituberculous drugs.

Although they are practical and satisfactory, serum microbiologic assays and in vitro drug susceptibility studies do require personnel and equipment which may not always be readily available. In an effort to determine whether appropriate and adequate antimicrobial therapy could be initiated without serum assays and drug susceptibility studies, the specific serum antimycobacterial activity test is being tried.

The test consists of giving the patient a loading dose of an antimicrobial agent. Six hours later serum is withdrawn aseptically and twofold serial serum dilutions are prepared in a Tween-albumin liquid medium to which is added a suspension of the *Mycobacterium tuberculosis* isolated from the patient's sputum. After five days, 2, 3, 5-triphenyl tetrazolium chloride (TTC) is added to each tube. If there is no change in the color of this indicator the growth of organisms has been impaired apparently by a biologically active drug in the serum, and it is presumed that the choice and dosage of the antimicrobial agent employed are both appropriate and adequate. The suspensions from those tubes in which bacteriostatic activity was displayed are then subcultured on oleic acid albumin agar medium to see whether a bactericidal effect has been achieved.

Serum microbiologic assay levels will be performed at the beginning of the study and the specific serum antimycobacterial activity test will be repeated at least once monthly until the sputum converts to negativity. Conclusions will be presented on the correlation between the laboratory results and the rate of sputum conversion and chest roentgenogram changes in approximately 100 pulmonary tuberculosis patients.

Some Current Concepts Concerning the Diseases of Connective Tissue. Harvey, A. McG., M.D., F.A.C.P., Baltimore, Md. (ML)

During the past few years much new information has been obtained regarding the immunologic aspects of the various diseases of connective tissue. These studies, together with the clinical observations relating to the association of more than one auto-immune disease in the same patient, and the detection of serologic abnormalities and related diseases in first-degree relatives of patients with certain of the connective tissue diseases, have led to new ideas concerning the pathogenesis. The implication of these findings for the internist will be discussed, with particular emphasis on the current concepts of the nature of systemic lupus erythematosus, rheumatoid arthritis, and other auto-immune diseases.

Enterococcal Endocarditis: A Report of Nineteen Cases with Long-Term Follow-up. Kaye, D., M.D.,* New York, N. Y., and Koenig, M. G., M.D.,* Nashville, Tenn. (CS)

Good results have been achieved in the therapy of endocarditis caused by penicillin-sensitive streptococci. However, the treatment of endocarditis caused by penicillin-resistant streptococci, usually of the enterococcal group, continues to be associated with a significant number of therapeutic failures. The present paper reviews the clinical data, therapy, and long-term follow-up of 19 patients with enterococcal endocarditis seen at The New York Hospital since 1945. The cure and long-term survival rate in this series compare favorably with those obtained in *Streptococcus viridans* endocarditis.

The female patients were of child-bearing age and the males were from an older age group. The most common portal of entry for the infecting micro-organism was the genito-urinary tract. Rheumatic heart disease was the most common underlying cardiac defect, but five patients had no apparent underlying heart disease. The clinical and laboratory manifestations were similar to those observed in endocarditis caused by penicillin-sensitive streptococci.

Despite in vitro resistance of enterococci to penicillin or to streptomycin, these two agents given simultaneously yielded a high rate of cure. Penicillin was unsatisfactory as the sole therapeutic agent, and despite in vitro sensitivity of enterococci to chlortetracycline, therapy with this antibiotic gave unsatisfactory results.

Sixteen patients (84%) were cured and 10 (53% of the original series) are still alive from five months to 13 years after treatment, with a mean survival time of 5.5 years.

Failure of treatment was related to delay in institution of adequate therapy and to the presence of heart failure, but was not correlated with the degree of penicillin or streptomycin resistance of the enterococci.

Pneumococcal Meningitis in the Adult: Clinical, Prognostic, and Therapeutic Findings in Forty-three Patients. Kirby, J. C., M.D.* Olsson, R. A., M.D.,* and Romansky, M. J., M.D., F.A.C.P., Washington, D. C. (CS)

During the 10-year period ending July, 1960, 43 patients with pneumococcal meningitis were encountered on our service. The majority were over 50 years of age. Meningitis was secondary to pneumonia in 16 patients and to otitis in eight. The spinal fluid smear was very reliable for early diagnosis, revealing the etiologic organism in 33 of 34 instances.

Factors having a bearing on prognosis were evaluated. The presence of associated pneumococcal infections, illness of over three days' duration, and coma were associated with a mortality of 75% or greater. Bacteremia, old age, blood count, spinal fluid cell count, or sugar concentration did not correlate with mortality. Therapy in 36 patients was broadly classifiable into penicillin alone (23 patients), erythromycin (six patients), and penicillin and one of the tetracycline group (seven patients). The mortality in the penicillin-treated group was 56%, that of the erythromycin group 50%, and 85.9% in the group treated with penicillin and a tetracycline.

Varicella Pneumonia. Mermelstein, R. H., M.D.,* and Freireich, A. W., M.D., F.A.C.P., Malverne, N. Y. (CS)

This communication reports the largest series to date of patients with varicella pneumonia and is the only large series without a mortality. Thirty-eight patients with chickenpox (adults over 13 years of age) were hospitalized at Meadowbrook Hospital from January, 1953, through July, 1960. Thirteen of them had typical x-ray findings of chickenpox pneumonia. The severity varied from five cases who were asymptomatic to several who were almost moribund.

Four cases are presented in detail, with x-rays and an accompanying table summarizing the salient features of the 13 cases. The clinical features are discussed with regard to course, treatment, prognosis, and laboratory findings.

This report serves to emphasize that the incidence of complicating pneumonia occurs in at least 35% of cases of adult varicella and is probably higher.

We have also pointed out that the severity of x-ray changes does not necessarily correlate with the observed clinical picture and that severe x-ray pneumonitis can coexist in patients without any respiratory symptoms.

Subacute Bacterial Endocarditis at the University of Minnesota Hospitals, 1939–1959. Pankey, G. A., M.D.,* Minneapolis, Minn.

One hundred sixty-seven patients with subacute bacterial endocarditis were observed at the University of Minnesota Hospitals from 1939 to 1959. Eleven patients had one recurrence and four had two recurrences. For analysis of clinical and laboratory data each recurrence was considered to be a separate patient, bringing the total number to 186. The disease was defined as a bacterial endocarditis of greater than 50 days' duration associated for the most part with a micro-organism of low virulence, resulting in clinical signs of chronic infection.

There were 85 males and 82 females. Thirty per cent were under 21 and 25% were over 50. Ninety-four patients had rheumatic heart disease and 35 had congenital heart disease, but no underlying organic heart disease was noted in 37 (22%). An autopsy was performed on 19 of the latter.

Upper respiratory infections and dental manipulations frequently were initiating factors. The most frequent abnormal physical and laboratory findings were murmur(s) (99.5%), fever (95%), increased ESR (94%), positive blood culture (83%) (most commonly *Streptococcus viridans*), cardiomegaly (75%), petechiae (70%), and anemia (64%).

Eighty-nine patients died in the hospital or within six months of discharge, giving a mortality of 53%. Before penicillin therapy (1939–1942) the mortality was over 80%, whereas during 1955–1959 it was 38%. An autopsy was performed on 60 of 72 patients who died in the hospital. An active endocardial lesion was found in 93% and was often associated with congestive heart failure, splenic and renal infarcts, pneumonia, glomerulonephritis, and encephalitis.

The importance of prophylactic antibiotics is stressed for all patients with known organic heart disease who undergo procedures that may give rise to bacteremia.

Cardiopulmonary Schistosomiasis. Rodriguez, H. F., M.D., (Assoc.), Duran, A. F., M.D.,* and Moliner, L. G., M.D.,* Ponce, P. R. (CS)

The most severe clinical manifestation of bilharziasis occurs when prolonged and extensive obstruction of the pulmonary arterioles by ova leads to pulmonary hypertension and cor pulmonale.

An analysis of 1,100 consecutive autopsies performed in four and one-half years disclosed 54 patients with *Schistosomiasis mansoni* of the liver and portal hypertension. Of these, 18 (33%) had pulmonary vascular obstruction of such degree as to produce bilharzial cor pulmonale. The clinical characteristics and results of radiographic and cardiac catheterization studies of these 18 subjects, as well as of seven additional living patients, will be discussed. The differentiating features from other conditions leading to similar findings will be presented, with special reference to rheumatic and congenital heart diseases.

In some areas where shunt surgery for portal hypertension due to hepatic schistosomiasis is being performed, a disappointing complication has appeared in certain cases. This consists of an aggravation of pre-existing pulmonary lesions and subsequent heart failure, caused by an increase in ova circulating through the pulmonary vascular tree following the portacaval anastomosis. This complication should be considered whenever shunt surgery is contemplated in patients already showing evidence of pulmonary hypertension.

It is felt that cardiopulmonary schistosomiasis has been neglected in the past in the medical literature. A greater awareness of the entity is of vital importance in view of the heavy migration of people from endemic schistosomiasis areas to the continental United States.

The James D. Bruce Memorial Lecture on Preventive Medicine: Eradication of Poliomyelitis. Sabin, A. B., M.D.,* Cincinnati, O. (CS)

The extensive field trials of 1959 on millions of susceptible persons of various ages not only established the safety and effectiveness of the oral, live poliovirus vaccine that I developed, but also suggested the possibility that the disease as well as the causative paralytic viruses could, under certain conditions, be completely eliminated. This is theoretically possible with the oral live vaccine, which gives rise to varying degrees of resistance to reinfection of the intestinal tract, but not with the killed virus vaccine, which, while protecting the individual against paralysis, does not prevent him from becoming a carrier.

The first steps in the attempt to eradicate poliomyelitis were taken in 1960 in many countries outside the U.S.A., where more than eighty-five million persons received the oral vaccine, and in the cities of Cincinnati, O., and Rochester, N. Y., in the U.S.A., where about 300,000 persons received this vaccine in community-wide programs. The results obtained in 1960 indicate that community-wide programs of sequential feeding of all three types of the vaccine during a period of several months can rapidly eliminate poliomyelitis. In Cincinnati, where about 75% of the children from three months to 18 years of age received the oral vaccine, there was not a single case of poliomyelitis in either the vaccinated or the unvaccinated in 1960, and 100% of the non-immunes who received the vaccine developed immunity. Furthermore, virologic studies indicated that the polio viruses practically disappeared from the community in about three months after administration of the last dose of the oral vaccine.

A program for the eradication of poliomyelitis in the U.S.A. by means of the oral vaccine would involve two phases: (1) community-wide immunization of the largest possible number of susceptibles in a single year during the winter and spring months, followed by (2) immunization of all newborn children during the first year of life as part of their regular medical care.

Candida Endocarditis: An Emerging Peril in Cardiovascular Surgery. Utz, J. P., M.D., (Assoc.), and Roberts, W. C., M.D.,* Bethesda, Md., Cooper, T., M.D.,* St. Louis, Mo., and Kravetz, H. M., M.D.,* and Andriole, V. T., M.D.,* Bethesda, Md. (CS)

Six patients with candida endocarditis were studied at the Clinical Center of the National Institutes of Health during a 21-month period. Five of these patients had had prior cardiac surgery, as had one of the 15 previously reported cases of candida endocarditis. An analysis of the clinical and pathologic features of these 21 cases revealed that *C. albicans* was the infecting organism in seven patients, *C. parapsilosis* in six, *C. guilliermondii* in four, *C. krusei* and *C. tropicalis* in one each. The responsible species was not given in two patients. Although candida endocarditis resembled bacterial endocarditis in most clinical aspects, the former was distinguished by the impressive frequency (eight of 21 patients) of embolism to larger arteries. Duration of illness ranged from two to 71 weeks, with a median of 13 weeks. Although all 21 patients died of their disease, those who received intensive antifungal therapy survived longer, regardless of the known relative pathogenicity of the species. Treatment with amphotericin B was transiently effective in reducing the colony count, and in rare instances in clearing the blood stream of candida organisms.

Fourteen of the 21 patients had received antibacterial therapy prior to superinfection with candida organisms. Because of this striking association, a study was undertaken to explore the role of antibacterial drugs in the pathogenesis of experimental candida endocarditis in animals. Five dogs were treated with penicillin and streptomycin following the surgical production of aortic regurgitation and intravenous inoculation with *C. guilliermondii*. Four of these animals developed positive blood cultures during life and three had endocarditis at autopsy. Positive blood cultures and autopsy evidence of endocarditis were not induced by surgery and inoculation alone in three animals not treated antibacterially or in three of four animals who received tetracycline alone. These studies suggest that candida endocarditis is a rare, but thus far fatal, complication of cardiac surgery. Furthermore, antibacterial therapy in man was *associated* with 14 of 21 cases of candida endocarditis and in animals was *essential* to the production of experimental candida endocarditis.

Antipenicillinase Activity of a New Synthetic Penicillin—Potassium α-Phenoxyethyl Penicillin. Waisbren, B. A., M.D., F.A.C.P., Milwaukee, Wis. (CI)

The fact that penicillin resistance of staphylococci is mediated through the production of the enzyme penicillinase rather than by the resistance of a vital enzyme system has led to many attempts to inhibit penicillinase so as to allow penicillin to destroy the still susceptible staphylococci. The antipenicillinase sera of Housewright and Henry failed in this regard because intracellular penicillinase apparently was not reached and destroyed.

Total synthesis of penicillin by Sheehan and Henery-Logan suggested the possibility that substances could be synthesized that would have the antibacterial activity of penicillin but that would be resistant to the action of penicillinase.

The observation of Bratchelor et al., that the addition of certain chemicals to brews containing penicillanic acid would result in the formation of antibacterial compounds closely related to penicillin G, has already led to the development of two useful "synthetic" penicillins and offers a method through which many others may be in the offing. In this study phenethacillin, 2,6-dimethoxyphenol penicillin, and penicillin G were compared in several in vitro parameters in regard to their activities against coagulose positive staphylococci: 2,6-dimethoxyphenol penicillin was the least affected by staphylococcal penicillinase; phenethacillin was least affected by *B. cereus* penicillinase; small inocula were most sensitive to phenethacillin, and penicillin G appeared to evoke the least persistors. Some potentiating effects of combinations of these agents were demonstrated. These data emphasize the limitations of any single method of comparison of antibiotics. However, when clinical comparisons of these agents have been completed, the in vitro tests most clinically applicable for use in the preliminary screening of new formulations of penicillin may be apparent.

Autoimmunity. Witebsky, E., M.D.,* Buffalo, N. Y. (ML)

Sensitization to a patient's own tissue constituents has been implicated in the etiology of several diseases in recent years. However, the justification for such an assumption in each case demands critical analysis. Thyroglobulin has been found to be auto-antigenic. In our hands, rabbit thyroglobulin incorporated into Freund adjuvants and injected intra-

dermally into normal rabbits produced circulating antibodies, as well as histologic changes in the thyroid gland of the immunized animal which resembled those of chronic thyroiditis in man. Also, thyroglobulin, when reinjected into the same rabbit, proved to be antigenic. The sera of patients suffering from chronic thyroiditis frequently were found to contain thyroglobulin antibodies. Therefore, by analogy, it is felt that chronic thyroiditis in man may be due to autosensitization against constituents of (his) the patient's own thyroid. Further studies are necessary to learn more about the trigger mechanism which would release intact thyroglobulin into the blood stream. Obviously other diseases of thus far unknown origin also may be due to autosensitization. In experimental animals it has been found that auto-antibodies can be produced against constituents of brain, spermatozoa, the adrenal and submaxillary glands, and other organs. To what extent these experimental findings will help in solving the mystery of certain diseases in man will depend upon further extensive investigation.

Pulmonary Disease

The Labile Properties of the Pulmonary Vascular Bed in Patients with Pulmonary Emphysema. Behnke, R. H., M.D., (Assoc.), Williams, J. F., Jr., M.D.,* and White, D. H., M.D.,* Indianapolis, Ind. (CI)

The factors which produce pulmonary hypertension in patients with pulmonary emphysema are poorly understood. The present study was undertaken in such patients to determine whether this vascular bed functions as a fixed rigid system or is labile as shown by pharmacologic alteration of its tone.

Patients with pulmonary emphysema, established by clinical and laboratory tests, who were free of congestive heart failure, were studied at rest and with steady-state exercise prior to and during infusion of acetylcholine (2 to 8 mg./min.) and isoproterenol (.005 to .010 mg./min.) with determination of wedge, pulmonary, and systemic arterial pressures and cardiac output (CO).

With acetylcholine at rest the pulmonary artery pressure (PA) fell in 11 of 13 (mean 4 mm. Hg), CO increased in 6 of 8 (0.3 to 1.4 L./min.), and systemic oxygen saturation decreased in 5 of 8 (mean 6.3%). With this drug and exercise 10 of 10 decreased their PA pressure (mean 5.8 mm. Hg), the CO increased in 4 of 7 (0.56 to 1.2 L./min.), and systemic oxygen saturation decreased in 4 of 7 (4.6%) over the exercise control.

Isoproterenol at rest decreased the PA pressure in 6 of 9 (mean 3 mm. Hg) while the CO increased in 4 of 7 (0.75 to 4.9 L./min.), and systemic oxygen saturation increased in 6 of 9 (3.6%). The pulmonary vascular resistance decreased in 5 of 5. This drug, given during exercise in seven, effected a fall in PA pressure in all patients (mean 7.5 mm. Hg), increased the CO in five (0.67 to 2.7 L./min.) and increased the systemic oxygen saturation in four (2.8%).

From these data it is concluded that the pulmonary vasculature in patients with pulmonary emphysema and hypertension has definite properties of vasomotion and lability. Too, that active vasoconstriction, both at rest and with exercise, is a factor in the maintenance of pulmonary hypertension and the development of cor pulmonale. It is conceivable that such a mechanism may also play a part in other states such as congestive heart failure.

The Management of Severe Pulmonary Emphysema. Lyons, H. A., M.D., F.A.C.P., Becker, W. H., M.D.,* Emmanuel, G., M.D.,* and Torres, G. E., M.D.,* Brooklyn, N. Y. (CS)

The increasing incidence of obstructive pulmonary emphysema in our population demands critical appraisal of its therapeutic management. The impression is common that patients who suffer from such an advanced respiratory problem, and who become comatose, are beyond aid. This attitude is not sound. The present study will demonstrate 15 severely ill comatose patients who were treated by tracheotomy, intermittent positive pressure breathing, oxygen, and antibiotics: they recovered and continued to live for periods varying from two to four years. Serial arterial blood gases and other pulmonary modalities will be discussed. Arterial oxygen saturations as low as 40% were seen, with recovery still being possible. Discussion of the level carbon dioxide tension and its relation to coma will be discussed. There are many factors other than the level of $PaCO_2$ alone which determine the comatose state; coma has been noted with a level of 60 mm. Hg and the absence of coma with levels as high as 96 mm. Hg. The physiologic contributions and the method of therapeutic operation of intermittent positive pressure breathing will be presented by illustrative nitrogen washout curves and pressure-volume studies.

A Study of Physiologic and Metabolic Changes in the Hyperventilation Syndrome. Saltzman, H. A., M.D.,* Sieker, H. O., M.D., (Assoc.), Heyman, A., M.D., F.A.C.P., Durham, N. C. (CI)

The syndrome of hyperventilation is observed frequently and is well recognized. Its pathogenesis, however, is not understood as well. It was the purpose of this study to elucidate the mechanism of the clinical syndrome with observations of respiratory function, biochemical changes, and electroencephalographic alterations during voluntary hyperventilation of one hour. Observations were made on eight normal students.

Voluntary hyperventilation decreased arterial carbon dioxide tensions (P_{CO_2}) to 15 to 25 mm. Hg within five minutes. The minute ventilation then decreased spontaneously and brief periods of apnea were observed. During the remainder of the study, the markedly hypocapnic levels were maintained with this respiratory pattern and only occasional interruption by five or six deep breaths. Most subjects noted drowsiness and a sense of unreality, but all remained conscious. The majority also demonstrated positive Chvostek signs but only two subjects developed tetany. During spontaneous apnea, arterial oxygen unsaturation was observed with values as low as 71%. The group mean for respiratory center sensitivity to carbon dioxide changed from 1.88 L./min. of ventilation per millimeter of Hg change in arterial P_{CO_2} prior to the study, to 0.79 L./min. per millimeter of Hg after one hour of hypocapnia. Serum calcium, potassium, ammonia, and sugar were essentially unchanged, but the mean for phosphorus fell from a control of 3.4 mg.% to 2 mg.%. The maximal electroencephalographic changes appeared shortly after the onset of hyperventilation and were characterized by diffuse high voltage, slow wave activity. These abnormalities were transient and reappeared only briefly during apnea.

These observations indicate that severe hypocapnia can be maintained without obvious overventilation once the arterial P_{CO_2} has been reduced. It is suggested that the sensitivity of respiratory regulatory centers to hypoxemia or carbon dioxide is reduced after prolonged hypocapnia. The striking decrease in serum phosphorus is unexplained. The transient nature of the electroencephalographic changes observed suggests that the central nervous system compensates rapidly during prolonged severe respiratory alkalosis.

Physiology and Management of Pulmonary Insufficiency due to Kyphoscoliosis. Stein, M., M.D.,* and Bruderman, I., M.D.,* Boston, Mass. (CI)

Detailed studies of pulmonary function were carried out in seven patients with severe thoracic deformity (kyphoscoliosis). The ages ranged from 31 to 79 years and included both acquired and congenital deformities. Six patients complained of moderate or severe dyspnea on mild exertion and five had histories consistent with cor pulmonale. The pulmonary function studies revealed vital capacities to be smaller than predicted, normal distribution of inspired gas, normal tidal volumes, alveolar hypoventilation, carbon dioxide retention, and arterial blood oxygen saturation disproportionately low for the degree of hypoventilation. On breathing 99.6% oxygen, plasma oxygen concentration failed to rise to predicted normal levels. One elderly female patient with severe kyphosis and a two-year history of dyspnea did not demonstrate the abnormalities of pulmonary function noted above. An excellent response to digitalis and diuretics indicated probable left ventricular failure as the genesis for her dyspnea. Another 31-year-old male patient was admitted with severe dyspnea in a moribund state. The use of tracheostomy and intermittent positive pressure breathing was particularly effective in reversing arterial oxygen unsaturation and hypercapnia. However, this therapy was not effective until a tracheostomy tube of 6.5 mm. intradermally was replaced by one of 10.5 mm. intradermally. This study extends the recent observations of Bergofsky, Turino, and Fishman (Medicine **38**: 263, 1959) and indicates that excessive venous admixture of kyphoscoliosis is due to a right to left shunt. The use of pulmonary function studies to differentiate dyspnea due to thoracic deformity from left ventricular failure and therapy in patients with severe kyphoscoliotic heart disease will be discussed.

Panlobular and Centrilobular Emphysema: Correlation of Clinical Findings with Pathologic Patterns. Sweet, H. C., M.D., F.A.C.P., Wyatt, J. P., M.D.,* Fritsch, A. J., M.D.,* and Kinsella, P. W., M.D.,* St. Louis, Mo. (CS)

Two distinct types of pulmonary emphysema have been recognized by post-mortem examination of the lungs by macrosection technics. Seventy-five such cases (39 centrilobular, 36 panlobular) have been subjected to clinical analysis. Centrilobular emphysema is characterized by distention and destruction of the central part of secondary lung lobules in-

volving the terminal respiratory bronchioles; panlobular (panacinar) by destruction of entire secondary lung lobules.

Clinically, three-fourths of centrilobular cases have an insidious onset with dyspnea preceded by cough. The patient is always underweight; blood pressure is normal or low; heart failure occurs in 50% and usually late in the disease. Roentgenographically, heart size is often small, the diaphragm depressed, bullae frequent. Pulmonary function studies reveal a normal or slightly increased total lung capacity, moderate elevation of alveolar nitrogen after oxygen breathing, and little air trapping as shown by (E to I)-(I to E) vital capacity differences. Post-mortem heart weight is often decreased. Average survival time is 10 years.

Onset of dyspnea is more abrupt in panlobular emphysema, and cardiac decompensation often accompanies the initial symptoms. The patient is frequently overweight; blood pressure is normal or elevated; heart failure occurs in 95% and earlier in the clinical course. Roentgenographically, the heart size is often large, the diaphragm less often depressed. Pulmonary function reveals a larger total lung capacity, less mixing impairment, and more marked air trapping. Total heart weight and right ventricular mass are often increased. Mean survival time is five years.

Analysis of the clinical features of panlobular and centrilobular emphysema has revealed differences which are of pathogenetic and therapeutic significance.

Renal and Electrolyte Disorders

Experimental Induction of Iso-Immune Hemolytic Anemia in Man by Transfusion of Unusually Potent Anti-Rh Antibodies. Bowman, H. S., M.D., F.A.C.P., Harrisburg, Pa., Mohn, J. F., M.D.,* and Lambert, R. M.,* Buffalo, N. Y., Brason, F. W., M.D.,* Harrisburg, Pa. (CI)

In an earlier study of experimental transfusion of donor plasma containing blood group antibodies into incompatible normal human recipients, a single ACD plasma containing exceptional anti-CD antibodies induced iso-immune hemolytic anemia in a C^wDe/Ce ($R_1{}^wR_1$) volunteer. The hematologic and immunologic observations made closely paralleled those found in naturally-occurring warm-antibody type acquired hemolytic anemia, and indicated that further detailed studies on additional recipients transfused with this unique anti-CD plasma might provide some insight into the pathogenesis of the spontaneously-occurring disorder.

The equivalent of a single unit of plasma of a sterile pool of three bleedings from the same donor was transfused into each of three normal male recipients of Rh groups CDe/cE (R_1R_2), cDE/cE (R_2R_2), and cde/cde (rr) respectively. At appropriate intervals before and after the plasma transfusions suitable specimens were drawn from these recipients to study chromium-51 red cell mass and survival; hematocrit, erythrocyte, reticulocyte, and spherocyte values; the erythroid: myeloid ratio and morphology of bone marrow; osmotic fragility of the erythrocytes; Fe^{59} plasma clearance and utilization; plasma hemoglobin, serum bilirubin, serum complement and haptoglobin levels; antibody sensitization of erythrocytes and levels of free, circulating antibody.

All incompatible recipients, including the $R_1{}^wR_1$, developed prompt erythrocyte sensitization which persisted at least 127 to 133 days. Temporary anemia was induced with mean red cell life of 4.7 to 5.1 days and contraction of circulating erythrocyte volumes; spherocytosis and reticulocytosis occurred. Fe^{59} utilization suggested that red cells within their four days after release from marrow were not appreciably destroyed, but thereafter were susceptible. Free, circulating antibody studies in at least one recipient indicated the possibility of transient auto-immunization.

The transfusion of such Rh antibodies into incompatible normal recipients thus may constitute a perfect model for investigating pathogenetic mechanisms of acquired hemolytic anemia and autoerythrocyte-sensitization in man.

The Limits of Renal Functional Adjustment in Uremia. Bradley, S. E., M.D., F.A.C.P., New York, N. Y. (CS)

The capacity of the kidney to adjust to various stressful conditions has been studied in patients with severe chronic renal insufficiency, secondary to chronic renal disease.

Changes in excretion of water, sodium, and potassium have been studied in relation to output of inulin and sodium para-aminohippurate during abdominal compression or assumption of the upright position. The results indicate a much more pronounced ability to alter urinary composition and volume than is evident clinically.

A Serological Reaction Associated with Sarcoidosis of Boeck. Chapman, J. S., M.D., (Assoc.), Dallas, Tex. (CI)

Sera of 33 patients with sarcoidosis or the benign hilar adenopathy syndrome have been studied by Ouchterlony double diffusion in agar. Antigens have consisted of defatted tuberculin-like material derived from type strains of anonymous *Mycobacteria.* These sera were obtained from several distinct geographic areas of the United States.

Twenty-eight of the 33 patients produced at least two bands against scotochromogenic antigens. Secondary reactions against photochromogenic and nonchromogenic antigens were found in a number of sera, but these reactions had a geographic variation corresponding to reported frequency of these organisms.

Three local patients when first seen possessed no detectable antibodies, but over a period of four to 12 months showed the reaction described. One local patient's serum contained no detectable antibody, but he produced a skin reaction of 20 mm. to scotochromogen alone of four mycobacterial and mycotic skin antigens.

Controls, comprising medical students and patients with tuberculosis, have shown either no reactions or entirely different patterns.

The Production of a Renal Lesion in Dogs by Injection of Plasma from Patients with Lupus Erythematosus. Clifford, G. O., M.D.,* and McClure, J., M.D.,* Detroit, Mich. (CI)

It has been reported that infusion of plasma from patients with systemic lupus erythematosus produces L.E. cells in some dogs so treated. We have infused plasma (average 60 ml.) from patients with systemic lupus erythematosus at various stages of activity and treatment. L.E. preps were positive in about half the patients. The animals were infused once or twice on alternate days and sacrificed three to 10 days later. Control animals were infused with plasma from normal patients.

A renal lesion was seen in the majority of animals given plasma from patients with systemic lupus irrespective of the presence or absence of a positive L.E. prep in the patients. This lesion consisted of hypercellularity and thickening of the glomerular basement membrane with "wire loops" suggestive of lupus nephritis. There were no other characteristic renal lesions and other tissues were uninvolved. These changes were not present in control animals.

In addition to the renal changes, approximately half the dogs treated with lupus erythematosus plasma developed peripheral blood manifestations (clot sieved technic) suggestive of L.E. cells (free cloudy nuclei, nuclear degeneration, atypical rosettes, and intense nucleophagocytosis), but classical L.E. cells were rare. These phenomena did not appear in control animals and were produced only by plasma from patients who had a positive L.E. prep.

These changes suggest that a factor in L.E. plasma is capable of producing lesions in organs of animals resembling those of the human disease.

Hyperguanidemia and Hypoglycemic Unresponsiveness in Renal Disease. Cohen, B. D., M.D.,* Spritz, N., M.D.,* Rubin, A. L., M.D.,* and Luckey, E. H., M.D., F.A.C.P., New York, N. Y. (CI)

Because of the occurrence of hypoglycemia in uremic patients during insulin and glucose treatment for hyperpotassemia a group of 20 patients with renal disease was studied with the standard insulin tolerance test. These were compared to 19 comparably ill patients free of renal disease. Although the initial hypoglycemia was identical a significantly delayed blood sugar was noted in the kidney disease group. These groups were re-examined using epinephrine and glucagon followed by periodic blood sugar determinations. The response to both tests showed a diminished glycolysis in the group with renal disease suggesting a deficiency in liver glycogen storage. In addition, abnormal glucose tolerance has been demonstrated in nondiabetics with renal disease. These paradoxic findings implicate an agent, accumulating in the presence of renal disease, which blocks hepatic glycogenesis. Plasma determinations of guanidine, methylguanidine, arginine, guanidinoacetic acid, creatine and creatinine revealed a significant elevation of the latter three in the patients with renal disease. The data support the contention that guanidinoacetic acid is a precursor of creatine and creatinine, and that guanidine and methylguanidine play no role in this metabolic pathway. Epinephrine and glucagon tolerance were subsequently carried out in a group of patients with creatinemia from causes other than kidney disease. The results showed a similarly diminished glycolysis suggesting that the retained guanides, members of a group of substances known to be effective in reducing liver glycogen, may play a role in the abnormal carbohydrate metabolism demonstrated in renal disease.

Electrolyte and Nitrogen Relationships in the Spirolactone-induced Natriuresis in Cirrhosis. Faloon, W. W., M.D., (Assoc.), and Ohanessian, S., M.D.,* Syracuse, N. Y., and Taylor, F. F., M.D.,* Watertown, N. Y. (CI)

The use of aldosterone blocking agents (spirolactones) for natriuresis in ascitic patients has been well demonstrated. Since low sodium and high potassium intakes stimulate aldosterone production the effect of variations in electrolyte intake upon the natriuretic effect of Aldactone (spironolactone) has been studied. In addition, by balance technics, the effect of this agent and of ascitic fluid mobilization upon nitrogen and electrolyte metabolism has been determined.

In four patients given spironolactone (400 mg. daily) and low sodium diets (10 to 20 mEq.), raising potassium intake from 80 mEq. daily to 160 mEq. increased sodium excretion by 50% or more with a subsequent decrease upon potassium withdrawal. In four patients receiving low sodium diets with spironolactone, reducing the daily potassium intake from 85 to 15 mEq. yielded a decrease in urinary sodium of 50% or more. Natriuresis was restored when the low potassium diet was supplemented with 78 mEq. of potassium. In two patients undergoing good natriuresis, addition of sodium to the diet reduced the net sodium loss and in one of these subsequent potassium supplementation did not completely restore the natriuresis.

In three patients receiving 800 mg. of spironolactone daily, nitrogen balance was unaffected during the six-day drug period with diuresis and weight loss. In the following six days, however, urine nitrogen increased by from 2 to 4 grams inducing negative balance. No consistent changes in potassium balance occurred during this nitrogen balance change.

These data indicate that the natriuresis of spirolactones is enhanced by low sodium, high potassium intakes, and decreased by the reverse. Induced diuresis is followed by increased urine nitrogen, perhaps related to the metabolism of ascitic fluid protein after resorption.

Pyelonephritis. Kass, E. H., M.D., F.A.C.P., Boston, Mass. (ML)

Pyelonephritis is a major problem in public health and preventive measures. The development of simple methods for the detection of asymptomatic bacteriuria and the demonstration that bacteriuria is often associated with or leads to the development of active pyelonephritis provides a simple tool for epidemiologic study of the natural history of bacteriuria.

Data will be presented to show that:

1. Infection of the urinary tract is one of the commonest infections in hospitals;
2. Bacteriuria occurs in four to seven per cent of pregnant women;
3. Bacteriuria precedes the development of pyelonephritis of pregnancy and that by the eradication of bacteriuria, pyelonephritis of pregnancy is prevented;
4. The prevalance of prenatal death and prematurity in bacteriuric women, and that by detecting and treating bacteriuria, a significant reduction in prematurity and perinatal death is possible;
5. Bacteriuria is found in four to six per cent of women in controlled random population studies in several parts of the world;
6. Bacteriuria is more commonly found in hypertensive than in nonhypertensive women; and,
7. The prevalence of bacteriuria is sufficiently great to make it likely that studies of hypertension in the future must take into account the presence of bacteriuria.

Acute Changes in Renal Excretion of Water and Solute in Patients with Laennec's Cirrhosis Induced by the Administration of the Pressor Amine, Metaraminol. Gornel, D. L., M.D.,* USNR, Loewenstein, L. M., M.D.,* Boston, Mass., and Lancestremere, R. G., M.D.,* and Papper, S., M.D., F.A.C.P., Richmond, Va. (CI)

In 1958, one of the authors (S. P.) presented to the Annual Session of the College clinical and experimental observations in patients with Laennec's cirrhosis who were dying with azotemia. Those studies suggested the possibility that the mechanisms of renal failure in these instances is of circulatory origin, rather than a parenchymal lesion.

Among a variety of attempts to alter renal circulation in this condition (characterized in part by decreased blood pressure) we studied the effects on renal excretion of the intravenous and intramuscular administration of the synthetic sympathomimetic amine,

metaraminol. Since similar mechanisms might also be operative in patients with cirrhosis without azotemia and with normal glomerular filtration rate (GFR), these patients were also studied.

Except for a few patients with marked depression of GFR, the administration of the drug was followed by striking augmentation in water diuresis, and marked increase in the rate of excretion of sodium, chloride, potassium, and total solute.

Normal subjects and patients with chronic renal disease did not exhibit similar response to the drug. While the mechanism of action of metaraminol in this study was not clear, the most likely explanation involves an alteration in circulatory phenomena different from the normal and the patient with primary chronic renal disease. Whether this alteration is operative through a direct or an indirect change in the kidney is not clear. All of the data are consistent with an increase in the rate of glomerular filtration alone although such increment was not consistently observed following the administration of the drug.

Post-transfusion Immunologic Purpura—A Newly Recognized Disease. Shulman, N. R., M.D.,* Aster, R. H., M.D.,* Leitner, A., M.D.,* and Hiller, M.C., M.D.,* Bethesda, Md. (CI)

A rare but serious hemorrhagic complication following blood transfusion, which heretofore had been indistinguishable from idiopathic thrombocytopenic purpura, was elucidated by finding in two patients who developed fulminant purpura one week post-transfusion, a high-titer antibody which reacted with platelets to cause complement fixation, agglutination, and inhibition of clot retraction. The antibody proved to be an iso-antibody which did not react with platelets obtained from both patients after recovery but reacted with platelets from most normal individuals. Quantitative reactions of the antibody with platelets from members of the patients' families and 300 donors selected at random showed that 74% of the population has homozygous reactive platelets, 24% heterozygous partially reactive platelets, and 2% homozygous nonreactive platelets (the patients' type). The reactive trait is an autosomal dominant.

Although approximately 2% of all transfusions are mismatched for this antigen, post-transfusion purpura is a relatively rare occurrence. Present studies suggest that the antigenic substance is usually fixed on donor platelets and does not gain access to antibody forming tissue of the recipient; but in some instances the antigen may become freed by disruption of platelets, for instance, by partial clotting of donor blood, and then may not only provoke antibody formation, but also coat the recipient's platelets to render them susceptible to the antibody which forms.

Recognition of this syndrome is of practical importance, for although the patients did not respond to steroid therapy and were not amenable to splenectomy, the disease was cured abruptly by performing an exchange transfusion to reduce circulating antibody.

Hereditary Nephropathy, Deafness, and Renal Foam Cells. Whalen, R. E., M.D.,* Huang, S., M.D.,* Peschel, E., M.D.,* and McIntosh, H. D., M.D., (Assoc.), Durham, N. C. (CS)

The association of renal disease and nerve deafness is now a well-recognized clinical entity. The hereditary nature of the deafness and renal disease, the increased severity of renal disease in males, and the occasional occurrence of ocular defects have been confirmed in over 20 families throughout the world. Whether the basic renal lesion is chronic pyelonephritis or glomerulonephritis remains to be elucidated. In three families large numbers of foam cells have been present in the kidneys.

The present report describes a family with hereditary nephropathy and deafness, and reviews some of the unusual pathologic features of the syndrome. Examination of the kidneys of the propositus of this family revealed a picture compatible with chronic glomerulonephritis. In addition, large numbers of renal foam cells were present.

In an effort to determine the significance and incidence of renal foam cells in the two forms of renal disease that have been considered the most likely pathologic process in hereditary nephropathy, 105 consecutive autopsy cases of chronic glomerulonephritis and 105 consecutive cases of chronic pyelonephritis were reviewed.

Foam cells were found in nine cases of glomerulonephritis and in six cases of pyelonephritis. Five of the nine cases of glomerulonephritis had a strong family of renal disease. Three of these five cases definitely had hereditary nephropathy. Only one of the six cases of pyelonephritis had any family history of renal disease.

Thus, although renal foam cells occur commonly in hereditary nephropathy, they are also found in other nongenetically determined forms of renal disease.

General

An Investigation of Factors Influencing the General Health of Presumably "Normal" Women. Hinkle, L. E., Jr., M.D., F.A.C.P., Christenson, W. N., M.D.,* Benjamin, B., M.D., (Assoc.), Kane, F. D., M.D.,* and Wolff, H. G., M.D., F.A.C.P., New York, N. Y. (CS)

To study the factors influencing the health of presumably "normal" people, 24 women, aged 22 to 39, were selected at random from 727 persons engaged in office work in two large rooms of a building in Manhattan and were studied weekly for six months by examinations, interviews, diagnostic tests, cultures, throat washings, serum samples, and photographs of the nose and throat. All recognizable episodes of illness were described and classified. Data on diseases present in the larger group, in the city and in families of participants; data on daily weather; data on general events affecting the whole population; data on diets, habits, and daily activities of participants; and data on their reactions to events and situations that they encountered, were independently derived and were assessed independently by investigators having no knowledge of rates of illness.

During the 180 days, each woman had from one to 14 impairments, from one to 9 chronic illnesses, and from 32 to 778 acute symptomatic episodes of illness, representing 22 to 50 syndromes involving nine to 14 of her organ systems and falling into six to 12 etiological categories. Each woman was partly impaired by illness from 1½ to 180 days, and disabled from zero to 18½ days. Sixty-eight per cent of episodes involved headaches, nasal vasomotor symptoms, myalgia, functional disturbances of the upper and lower gastrointestinal and the genitourinary tracts, and periods of anxiety and tension, usually of less than one-half day's duration. However 28% of episodes lasted longer than two days, involved many organ systems and apparent causes, and included illnesses such as bronchitis, peptic ulcer, menorrhagia, osteoarthritis, eczema, and a serious depressive illness. Infections of the respiratory and gastrointestinal tracts accounted for most of the transient, disabling illnesses but for only 5.6% of all episodes of illness.

The "most ill woman" had 24 times as many episodes of illness, was twice as impaired, and experienced a risk of death from illness estimated at 100 times as great as that of the "least ill woman." Except for acute infectious episodes, the amount of illness experienced by a woman was not significantly influenced by the illnesses of the larger group, or by transient changes in her environment, her food intake, her daily activities, her emotions or her life situation; but it was significantly correlated with the amount of illness she had experienced in the past and with the overall situation in which she was living during the observation period. Those women living in situations evaluated as more burdensome, demanding, depriving, and conflict-inducing for them consistently displayed more of all types of illness, were more impaired and experienced greater risk of death because of illness. The factors most important in determining the general health of these women appear to have been in existence at the beginning of the observation period, and to have remained relatively unchanged throughout it.

The Chemotherapy of Neoplastic Diseases. Ross, J. F., M.D., F.A.C.P., Los Angeles, Calif. (ML)

Never in the history of mankind has an effort to control disease equalled the tremendous attack now being made upon the nature, cause, and cure of cancer. Hundreds of millions of dollars and the efforts of thousands of investigators are being devoted to the study of cancer and to methods of treatment. A major portion of this program is directed to the development of chemotherapeutic methods of control of neoplasia. Vast numbers of substances ranging from crude plant and animal tissue extracts to carefully designed synthetic chemical compounds are being tested for their effectiveness as cancerocidal or cancerostatic agents.

What are the results to date of these chemotherapeutic studies? What have they contributed to our ability to control cancers? What reasonably can be expected of cancer chemotherapy in the future?

BOOK REVIEWS

Clinicopathological Conferences of the Massachusetts General Hospital. By BENJAMIN CASTLEMAN, M.D., and H. ROBERT DUDLEY, JR., M.D. 289 pages; 27.5 × 21.8 cm. Little, Brown and Company, Boston, 1960. Price, $12.50.

For over 35 years *Case Records of the Massachusetts General Hospital* have appeared each week in *The New England Journal of Medicine* and have given pleasure and knowledge to the readers of this distinguished journal. These *Records* have been put to a variety of uses, many certainly not foreseen by their compilers. A specialist in electronic computation and analysis, Robert Ledley, has used them in a study of the logical basis of medical diagnosis. A biochemist, Halvor Christensen, has set them up as interpretive exercises for students in his textbook, *Diagnostic Biochemistry.* They are cited in bibliographies in the medical literature of the world. And certainly they must serve widely as foils for countless players of one-upsmanship who strive weekly to outwit the best clinicians of Boston.

The appeal of the *Case Records* lies not in the excessive rarity of the problems they present, nor in the contest of the clinician against the pathologist, but in their constantly lucid demonstrations of diagnostic logic. Although in some of the *Cases,* as in *Case 35* of this collection (an instance of the milk-alkali syndrome, discussed by Dr. Alexander Leaf) the clinical analysis rests heavily on the interpretation of blood chemical values, in most of the *Cases* the diagnostic conclusions are drawn from bedside data interpreted against a wide background of bedside experience. Though this approach to diagnosis is the hardest to teach (because it demands of the teacher long and broad experience), it is the approach the physician must learn. Without this skill he will err appallingly often in his diagnoses or will waste his patient's time and money with zigzags from the clinical laboratory to the x-ray department and back. The earliest *Case* selected for this collection, an instance of metastatic hypernephroma discussed by Dr. Walter Bauer, appeared in *The New England Journal of Medicine* in 1936, but most of the *Cases* were first published after 1945. Addenda placed at the end of each *Case* remind the reader of diagnostic or therapeutic points of view which have developed since the original publication of these *Cases.* The value of this collection is further enhanced by illustrations of roentgenographs, electrocardiographs, and pathologic specimens, as well as by an index which gives references to clinical and pathologic diagnoses. The book is well-printed and sturdily bound.

For whom was this collection published? For the alumni of Massachusetts General Hospital, the cynic might reply, now laboring in less celebrated and august institutions, that they might have a tangible souvenir of their golden days. No, this work is for any physician, no matter his age, who knows that his learning is never complete. He cannot and will not turn to the mammoth textbooks of medicine for refreshment, but he can read these *Cases,* perhaps one each night or one each week, and recall with pleasure aspects of clinical medicine he once knew well.

To the editors of *The New England Journal of Medicine,* one question: Now that Drs. Castleman and Dudley have prepared this tasty potpourri from your pages, when can we expect to see annual collections of the *Medical Progress* articles? If one feature of this journal must be selected as most valuable, this is the one. These *Progress* reviews are the most consistently thorough, well-written, and eminently readable surveys of their kind. But for our delight, unadulterated with earnest

teaching, give us an anthology of those short, witty, and waggish editorials which are your signature. Let the selection open with "The Wearing of the Genes" and close with "Divine Afflatus."

EDWARD J. HUTH, M.D.

Bleeding Syndromes: A Clinical Manual. By OSCAR D. RATNOFF, M.D. 287 pages; 23.5 × 16 cm. Charles C Thomas, Springfield, Ill., 1960. Price, $8.50.

Dr. Ratnoff has set out to write a book on the bleeding syndromes that can be used by a nonspecialist in the field of blood coagulation. He has done an admirable job. The book deals with the clinical problems facing practitioners of medicine. Dr. Ratnoff adequately goes into the pathogeneses, diagnoses, and treatment of these diseases.

Technical sections are omitted, as well they may be, because the several other standard reference books on blood coagulation deal with this aspect of the bleeding diseases very thoroughly. An extensive bibliography of over 700 references is presented for more detailed aspects of the problem. At the end of each chapter selected references are given. This is an excellent idea and should be of great help to those who are not very familiar with this field.

Most of this work comes from Dr. Ratnoff's own experience in taking care of patients with bleeding diseases, and the nonspecialist can use this great experience in his own practice. This reviewer does not agree with all of Dr. Ratnoff's statements, but this is to be expected in the area of coagulation problems. Of course, this does not detract from the worth of the book. Several references are incorrectly given, but these will probably be corrected in subsequent editions.

Dr. Ratnoff's book is highly recommended for all who want the latest knowledge in caring for the patient with a bleeding disease.

HAROLD A. WURZEL, M.D.

Neurovascular Compression Syndromes of the Shoulder Girdle. By LOUIS M. ROSATI, M.D., and JERE W. LORD, M.D. 168 pages; 23 × 15.5 cm. Grune & Stratton, N. Y., 1960. Price, $7.25.

On a size and weight basis, this slim volume is over-priced at $7.25. However, the information contained herein will be of great value to any physician who is confronted with the perplexing diagnostic problem of pain about the shoulder girdle and upper extremities. This includes all physicians who must treat diseases of the cervical spine, vascular abnormalities of the upper extremities, and neurologic syndromes of the brachial plexus and peripheral nerves. The book is very lucidly written and the illustrations, including some by Netter, are all instructive and clear.

The authors explain the mechanics of motion about the shoulder girdle and the means by which compression of the subclavian artery, of the cords of the brachial plexus, or of both, occurs in the hyperabduction, scalenus anticus, and costoclavicular syndromes. They elaborate upon the need for a physical examination in which arm position and shoulder motion, and their effects upon the precipitation of symptoms and signs, are studied.

Future editions of this worth-while volume might include a discussion of the frequency with which arm pulses can be obliterated in the asymptomatic population. This positional decrease in pulse creates a diagnostic dilemma in patients with atypical cervicobrachial pain syndromes. Does their pain relate to hyperabduction or to costoclavicular compression simply because the peripheral pulse decreases in certain arm positions?

JAMES F. TOOLE, M.D.

Cutaneous Manifestations of the Reticuloendothelial Granulomas. Edited by SAMUEL M. BLUEFARB, B.S., M.D., F.A.C.P., with an introduction by FRANK C. COMBES, M.D. 410 pages; 22 × 14.5 cm. Charles C Thomas, Springfield, Ill., 1960. Price, $14.50.

Dermatology is a part of internal medicine, and internal medicine is a part of dermatology. This mutual dependence is an unstated theme in this new monograph. The reticuloendothelial granulomas confront the internist with disorders of internal organs and the dermatologist with lesions of the skin. Each specialist must know something of the other's concern if he is to reach full competence in his own field when considering these diseases.

Of the four chapters in the book, three are written largely from the dermatologic viewpoint, and tend to be concentrated on the skin lesions of some generalized disorders. Dr. Frederick Uhrbach's chapter, the first, is a concise account of the *Lipoidoses,* covering such disorders as Gaucher's disease, essential familial hypercholesterolemia, xanthomatous biliary cirrhosis, and related diseases. The second chapter, by Dr. Bluefarb, takes up *The Systemic Reticuloendothelial Granulomas,* or Letterer-Siewe disease, Schüller-Christian disease, and eosinophilic granuloma of the bone—all three probably clinical variants of the same disorder. Drs. Israel, Beerman, and Sones summarize the present views of *Sarcoidosis* in the third chapter. Each of these three chapters is a competent if not exhaustive review of its topic. These chapters do not present the visceral manifestations in complete detail and hence are not reason enough for the internist to buy this book. For example, although the chapter on *Sarcoidosis* contains a good selection of pictures of the skin lesions, both in gross appearance and in histologic detail, the characteristic bone lesions are not illustrated and the radiographs of the chest lesions are so small as to be virtually useless.

The last chapter, on *Mastocytosis* (*Urticaria Pigmentosa*), by Dr. Felix Sagher and Mr. Zvi Even-Paz, is clearly the best. The disease it describes in admirable and exhaustive detail is little known to internists because only in the past decade has the systemic aspect of this disorder become clearly recognized. The systemic lesions develop in the lymph nodes, hemopoietic system, liver, spleen, and bones. The osseous lesions show themselves in many guises—osteoporosis, osteosclerosis, "punched-out" lucencies, and pagetoid changes (mixed lytic and blastic areas). The hematologic disorders include leukocytosis of all degrees, leukopenia, lymphocytosis, monocytosis, anemia, thrombocytopenia, and hemorrhagic diatheses not clearly related to platelet deficiency. If the skin lesions were always present in this disease, the internist might yield the right of diagnosis to the dermatologist. But in the past two years an entirely systemic form of mastocytosis has been described. Hence the internist cannot, in good conscience, remain ignorant of this disease. He will probably find no better complete account of mastocytosis than this one. The skin, bone, and visceral lesions are generously illustrated with good photographs, roentgen films, and histologic preparations; the bibliography is longer than those of the first three chapters together. The internist may hesitate to pay the price of this book, but if he has a special interest in hematologic and osseous diseases he must read the chapter by Sagher and Even-Paz.

E. J. H.

Letters to My Son. By WENDELL J. S. KRIEG, M.D. 82 pages; 15.8 × 10.8 cm. Brain Books, Box Nine, Evanston, Ill., 1960. Price, $3.00.

Dr. Krieg, an eminent neuroanatomist writing as a father to a fictional son, gives his view of academic life in the medical sciences. After a few words on the common observation that professors earn less money than practitioners, he considers the demands placed upon the teacher and investigator, and how to prepare for these tasks. After his fictional son has gotten an appointment, Dr. Krieg advises him on such matters as how to choose research topics, how to write papers, and how to enjoy wine, women, and art on a modest income.

His *Letters,* written with the sophistication of a Lord Chesterfield, are blunt and candid; they never carry the bland and platitudinous tone of a Polonius. His style is polished and many of his sentences carry epigrammatic force. His advice, in places, may sound cynical to some pious readers, but to the honest ones it will be refreshingly frank.

Though Dr. Krieg's words are mostly those of advice, he also consoles those who do not climb, despite their excellence:

> "Your reputation is based on merit, but your advancement depends partly on the personal traits of yourself and your chief, and their interaction. It would be best if we could devise a boss who is congenial to our temperament and who appreciates our qualities. This is rarely done, but if a boss chooses you, it can amount to the same thing. Bad luck it is when the man who selected you goes away and leaves you as a legacy, for the new chief may not care for your type, and your best efforts are in vain."

Every man who hopes to spend his life in academic medicine, and every man now so engaged, should get Dr. Krieg's book and read it three or four times. Then he should pass it up to the chairman of his department, who may have forgotten what is going on three levels down.

One little exception must be taken to the quality of Doctor Krieg's book. He has "exercised (his) hobby of typographical decoration" in its production, but with unpleasant results. The first and last pages of all chapters are garnished with ornaments, printers' flowers, and similar gee-gaws, which clash with the workaday roman type face of the text. And, compounding the discord, the chapter headings are in copperplate script, while the phrase, "My dear Son," appears in a loose form of a chancery hand. These flaws in typography will offend a few, but they detract in no real way from the excellence of Dr. Krieg's advice.

E. J. H.

Atlas of Exfoliative Cytology: Supplement 2. By GEORGE N. PAPANICOLAOU, M.D., PH.D. 94 pages; 28 × 20.5 cm. Published for The Commonwealth Fund by Harvard University Press, Cambridge, Mass., 1960.

This supplement is intended as an insert for the original *Atlas.* It contains 16 color plates and expands material previously presented, particularly in the section on gastric cytology. New sections are presented on cells in spinal fluid and on tumor cells circulating in the peripheral blood. A plate showing confusing cells found in smears from patients with condyloma acuminatum is a welcome addition. A modification of the original staining procedure is presented. We have tried this and it is highly satisfactory, particularly for cells in effusions. As Dr. Papanicolaou points out, this is not a textbook but a guide for cytologists. It is an atlas in the strict sense of the word and a must for laboratories of cytology.

H. T. ENTERLINE, M.D.

Manual of Care for the Disabled Patient. By ARTHUR J. HEATHER, M.D. 119 pages; 21.5 ×14.5 cm. The Macmillan Company, New York, 1960. Price, $3.75.

A patient's return to a useful and happy life may be due less to diagnostic skills brought to his disease than to some practical help from his physician. Dr. Heather has described the methods by which patients with hemiplegia, spinal cord lesions, arthritides, osteoporosis, and amputations can be helped to overcome the problems imposed by these disorders. He has not described the care of those disabilities, aside from loss of limbs, which follow surgical treatment—for example, colostomies and colonic "bladders." These omissions may be due to his bias as a physiatrist.

The text has been padded with some material not clearly pertinent. The compilations of causes of strokes and of leg lesions leading to amputation add nothing to the chapters in which they appear. The illustration (Figure 9-2A) in the chapter on osteoporosis of an x-ray which shows *no* renal calculi is pointless.

The discussion of nutrition is weak in some details. "Routinely (giving) patients in a rehabilitation center" as many as three multivitamin capsules daily will usually be a waste of money and of medication. In discussing the tube feeding of comatose patients with stroke, Dr. Heather neglects to mention the hazard of using a formula excessively rich in protein and salts. This practice presents excessive solute to the kidney for excretion, and the comatose patient, unable to demand more water, may develop severe dehydration.

Despite omissions, some padding, and other minor flaws, Dr. Heather's book is a useful, practical manual. It presents measures which every physician should be able to use in the care of his patients. These practical matters are too often neglected in the medical curriculum.

E. J. H.

Man and His Body. By BENJAMIN F. MILLER, M.D., and RUTH GOODE. 361 pages. Simon & Schuster, New York, 1960. Price, $5.95.

Can the layman be brought to appreciate the countless subtle mechanisms of the human body? Dr. Miller and Mrs. Goode must believe he can, for this is the aim of their work. They have tried to describe the structure and function of the body at all levels of organization, from the molecular to the mental. In their account they have not simply reduced conventional texts of physiology to a gruel for the reader untrained in biology, but have brought to him that awe and excitement felt by every sensitive physician when he reflects on the complexity of his body.

The authors have used many of the devices a writer might choose for popularization. Biological processes are compared to mechanical devices (analogy). The homeostatic circuits of action and reaction are described in terms of purposeful protections (teleology). And the descriptive text is relieved at many points with historical anecdotes, drawn from medical research in this century and the last.

With the completion of this book, Dr. Miller must be counted as one of the small and skillful group of biologists and physicians who have succeeded in telling, in a responsible way, the complex story of man's body for the layman. This success is no small glory in our age when even minor and tentative advances in medicine are exploited recklessly by irresponsible segments of the press. Dr. Miller has shown his skill and responsibility in three previous works, *You and Your Doctor, When Doctors are Patients,* (an anthology), and *The Complete Medical Guide.* In the present book, his use of the art of writing joined to his knowledge of biology and medicine puts him into the company of Thomas Huxley, H. G. Wells, Julian Huxley, Howard Haggard, and Logan Clendening. Compared to the writing of these five, his is most like that in some of the essays of the earlier Huxley (Thomas), though

not so simple, forceful, and direct. The likeness shows clearly in a passage which is a parallel to one in Huxley's *Lessons in Elementary Physiology*. Huxley wrote:

> "The sun's rays, acting through the vegetable world, build up some of the wandering molecules of carbonic acid, of water, of ammonia, and of salts, into the fabric of plants. The plants are devoured by animals, animals devour one another, man devours both plants and other animals; and hence it is very possible that atoms which once formed an integral part of the busy brain of Julius Caesar may now enter into the composition of Caesar, the Negro in Alabama, and of Caesar, the house dog in an English homestead."

Dr. Miller writes:

> ". . . We knit together time. . . . With each breath we take into our bodies a thousand million million atoms . . . of oxygen. These atoms of the life-giving gas in our earth's atmosphere are virtually indestructible, and so it may well be that in some of the oxygen you breathe today there may be the same atoms that coursed through the blood of Washington, of da Vinci, of Caesar and Cleopatra, of Cheops the pyramid builder, perhaps of the first man who lifted his gaze upward at night and wondered about the stars."

Although Dr. Miller and Mrs. Goode have aimed their work at the layman, many physicians, too busy for years with mundane concerns of practice to reflect on the awful complexities and precision of the body's devices, may profit from reading this book. And physicians who wish to encourage gently a nephew or a neighbor's son to enter medicine may find in this book an aid to that end.

E. J. H.

Médecine Sociale de l'Adolescent. Sa Mise au Travail. Edited by Prof. Louis Christiaens. 614 pages; 25 × 16.5 cm. G. Doin et Cie, Paris, 1960. Price, NF 54.

While the adolescent in the United States sweats at raising the horsepower of his hot-rod jalopy, his French equal is likely to be at work in industry. No matter the nationality or employment, adolescents everywhere have problems, most commonly emotional, but often physical. But compared to children with their infectious diseases and to adults with their degenerative disorders and malignancies, adolescents are usually regarded as representatives of the prime of life—at least in the biologic sense. Hence, until recently, physicians have taken little formal notice of this age as one with its peculiar problems.

Dr. Christiaens, with the collaboration and help of 10 other physicians, has written a textbook of medicine aimed at doctors especially concerned with the detection, treatment, and prevention of disease in adolescents. As the title implies, he considers here not only the diseases usually taken as the special province of internal medicine or of pediatrics, but the full range of medical concerns: mental deficiency, emotional disorders, orthopedic disabilities, and the hazards of sports. All of these matters are considered, in addition, from the viewpoint of the occupational or industrial physician. The material presented is mostly a synthesis of French views, although some of the diagnostic methods discussed are based on American technics.

No American textbook is a close counterpart to this work, although Roswell Gallagher's recent textbook on adolescent medicine covers some of the same ground.

The book lacks an index, but this deficiency is partly covered by a detailed table of contents.

E. J. H.

American Drug Index, 1961. By CHARLES O. WILSON, Ph.D. and TONY EVERETT JONES, PH.D. 791 pages; 21 × 14 cm. J. B. Lippincott Company, Philadelphia, 1961. Price, $6.75.

In this unique handbook, drugs and drug combinations are listed alphabetically by generic and trade names. Each entry by generic name includes an indication of the status of acceptance of the drug (*U. S. Pharmacopeia* or *New and Nonofficial Drugs*) and its chemical and trade names. Entries under trade names include the generic drug name or names (for combinations) as well as the dosage forms and package sizes available. Special tables of combination forms, giving details of composition, are placed at the appropriate alphabetical positions under generic name headings. The entries give no information on modes of drug action, none on side effects and toxicities, and only the briefest mentions of drug uses.

The enormous variety of drug combinations listed is at once a tribute to and an indictment of American pharmacy. For example, 70 combinations containing rutin are listed in one table. The physician who wants to prescribe rutin combined with other drugs, such as mannitol hexanitrate, phenobarbital, and others, can be happy that so many choices are at hand. But even if he wants to prescribe 20 mg. of rutin—a drug of doubtful value—and 15 mg. of phenobarbital for a patient, why should he give both in a single pill? The patient may need more phenobarbital than the 15 mg. dose for an adequate sedative effect. Shall the physician then give a second 15 mg. tablet of phenobarbital as a supplement? Or is he to double the dose of the combination tablet? If he decides on the first choice, the patient must take two tablets anyway, and with the second choice, the patient pays for additional rutin not needed. Obviously the production and promotion of multi-ingredient drug forms is not the fault of the authors of this compendium. I can only hope that they feel pain at having to list such products for the sake of completeness.

The physician will find two uses for this book: the identification of drugs the patient has been given by other physicians and known to the patient only by trade name; and guidance in choosing a preparation (by trade names and dosage forms) of a drug he has not recently prescribed. The *American Drug Index* is not a guide to the proper use of drugs and cannot be used instead of handbooks like *New and Nonofficial Drugs.* It is a practical catalogue of drugs and drug combinations now made and sold in the United States; as such a catalogue it is complete, concise, and unsurpassed.

EDWARD J. HUTH, M.D.

BOOK NOTICES

Culture Methods for Invertebrate Animals. By PAUL S. GALTSOFF, FRANK E. LUTZ, PAUL S. WELCH, JAMES G. NEEDHAM, Chairman, and other contributors. 590 pages; 20.3 × 13.5 cm. Dover Publications, Inc., New York, 1960. Price, $2.75.

This well printed and inexpensive manual is described nicely by its title. Experimentalists, medical and biological, should find it very useful indeed.

Physicians with sons bent to biology will be thanked by them for bringing a copy home. But, fathers, heed this warning—your son may wish to make of you, your own flesh, a feeding station for hog lice (p. 296), and if those vials which "must be worn continuously under the clothing" drop to the floor by a patient's bed, your practice may suffer. And mother may object to housing colonies of termites, cockroaches, and carpet beetles under the family roof.

E. J. H.

Erkrankungen der Leber und der Gallenwege. By DR. I. MAGYAR, Institut für Ärztliche Fortbildung, Budapest (in two volumes). Vol. I: 467 pages; 24.5 × 17.5 cm.; Vol. II: 351 pages; 24.5 × 17.5 cm. Akademie-Verlag, Berlin, 1959.

After devoting four chapters in Volume I to the clinical and laboratory manifestations of diseases of the liver and biliary tract and to methods for study of these diseases, Dr. Magyar gives a detailed account of acute and chronic hepatitides due to various causes. Volume II covers cirrhosis, hepatic lesions of generalized disease, and disorders of the gall-bladder and bile ducts. Individual chapters discuss therapy for hepatitis and cirrhosis. Bibliographies follow each chapter, and an index appears at the end of Volume II. References are taken from the European and American literature.

E. J. H.

Index-Handbook of Cardiovascular Agents. Vol. 2 (in two parts). Publication No. 281 of the National Academy of Sciences, National Research Council, Washington, D. C. Compiled under the direction of ISAAC D. WELT, Director, Cardiovascular Literature Project. 1,568 pages (Parts I and II); 28.5 × 23 cm. (both volumes). National Academy of Sciences, National Research Council, Washington, D. C., 1960. Price, $15.00.

For the medical scientist who needs data from the literature on a narrow question, the conventional sources, such as *Index Medicus,* are only places to start his search. He must gather his bibliography from under a few general headings and then labor through each paper to see whether it contains the data pertinent to his inquiry. This *Index-Handbook* solves the problem in the field of cardiovascular pharmacology. The first volume released, Volume 2, covers the world literature for the years 1951–1955. Volume 1 will cover 1931–1950, and Volume 3, 1956–1960.

The first section of this handbook is a list of articles indexed, arranged, and numbered in order of acquisition. The second section is an author index. The subject index is the third section. Here entries are arranged under alphabetized topic headings, and each entry is, in effect, a concise abstract. The analytical thoroughness of the subject index exceeds by far that of conventional sources.

This compilation will be an invaluable reference source for all students of cardiovascular physiology and pharmacology.

E. J. H.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. So far as is practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

American Drug Index, 1961. By CHARLES O. WILSON, Ph.D. and TONY EVERETT JONES, Ph.D. 791 pages; 21 × 14 cm. J. B. Lippincott Company, Philadelphia, 1961. Price, $6.75.

Aspects of Public Health Nursing. World Health Organization Public Health Papers No. 4. 185 pages; 21 × 14 cm. Published by the World Health Organization, Geneva, 1961. Price, $1.75 per copy (paper-bound).

Cardiovascular Dynamics. 2nd Ed. By ROBERT F. RUSHMER, M.D., Professor of Physiology and Biophysics, University of Washington Medical School. 503 pages; 26 × 17 cm. W. B. Saunders Company, Philadelphia and London, 1961. Price, $12.50.

Cell Physiology of Neoplasia. Edited by the Staff of the University of Texas and the M. D. Anderson Hospital and Tumor Institute. 653 pages; 24 × 15.5 cm. University of Texas Press, Austin, 1961. Price, $10.50.

Clinical Use of Radioisotopes. A Manual of Technique. Edited by THEODORE FIELDS, M.S., F.A.C.R. (Assoc.) and LINDEN SEED, M.D., with 18 contributors. 475 pages; 19.9 × 13 cm. The Year Book Publishers, Inc., Chicago, 1961. Price, $10.50.

Culture Methods for Invertebrate Animals. By PAUL S. GALTSOFF, FRANK E. LUTZ, PAUL S. WELCH, and JAMES G. NEEDHAM (Chairman), with other contributors. 590 pages; 20.3 × 13.5 cm. Dover Publications, Inc., New York, 1960. Price, $2.75.

Current Therapy—1961. Edited by HOWARD F. CONN, M.D.; Consulting Editors: GEORGE E. BURCH, M. EDWARD DAVID, VINCENT J. DERBES, GARFIELD G. DUNCAN, HUGH J. JEWETT, CLARENCE S. LIVINGOOD, PERRIN H. LONG, H. HOUSTON MERRITT, WALTER L. PALMER, HOBART A. REIMANN, RALPH WAYNE RUNDLES, and ROBERT H. WILLIAMS. 806 pages; 27.5 × 20.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $12.50.

Eighth Report, Expert Committee on Malaria. World Health Organization Technical Report Series No. 205. 50 pages; 24 × 16 cm. Published by the World Health Organization, Geneva, 1961. Price, 60¢ per copy (paper-bound).

Expert Committee on Addiction-Producing Drugs. Eleventh Report. World Health Organization Technical Report Series No. 211. 16 pages; 24 × 16 cm. Published by the World Health Organization, Geneva, 1961. Price, 30¢ per copy (paper-bound).

The Great Epidemic. By A. A. HOEHLING. 217 pages; 21 × 14 cm. Little, Brown and Company, Boston, 1961. Price, $3.95.

Haematology and Blood Groups. Papers from the British Medical Bulletin. Edited by D. A. G. GALTON and K. L. G. GOLDSMITH. 169 pages; 28.5 × 22 cm. The University of Chicago Press, Chicago. 1961. Price, $4.00.

Handbook of Physiology. 43rd Ed. By R. J. S. MCDOWALL, M.D., D.Sc., M.R.C.P. (Lond.), F.R.C.P. (Edin.). Emeritus Professor of Physiology, University of London. 759 pages; 24 × 16 cm. J. B. Lippincott Company, Philadelphia. 1961, Price, $12.50.

Human Factors in Jet and Space Travel: A Medical-Psychological Analysis. Edited by S. B. SELLS, Ph.D., Professor of Psychology, Texas Christian University, and CHARLES A. BERRY, M.D., Lt. Col. (USAF) MC, Chief, Flight Medicine Branch, Aerospace Medicine Division, Office of the Surgeon General, USAF; with a foreword by OLIVER K. NIESS, M.D., Maj. Gen. (USAF) MC. 386 pages; 24 × 15.5 cm. The Ronald Press Company, New York. Price, $12.00.

Index-Handbook of Cardiovascular Agents. Vol. 2 (in two parts). Publication No. 821 of the National Academy of Sciences, National Research Council, Washington, D. C. Compiled under the direction of ISAAC D. WELT, Director, Cardio-

vascular Literature Project. 1,568 pages (Parts I and II); 28.5 × 23 cm. (both volumes). National Academy of Sciences, National Research Council, Washington, D. C., 1960. Price, $15.00 (both volumes).

Kernicterus. Report Based on a Symposium Held at the IX International Congress of Pediatrics in Montreal, July, 1959. Edited by ANDREW SASS-KORTSÁK, M.D. 221 pages; 24 × 16 cm. University of Toronto Press, Toronto, 1961.

Mathematical Biophysics: Physico-Mathematical Foundations of Biology. Vols. 1 and 2. 3rd Ed. (revised). By N. RASHEVSKY. Vol. 1: 488 pages; 20.3 × 13.5 cm.; Vol. 2: 462 pages; 20.3 × 13.5 cm. Dover Publications, Inc., New York, 1960. Price, $5.00 (both volumes).

Médecine Social de l'Adolescent: Sa Mise au Travail. Edited by LOUIS CHRISTIAENS. 614 pages; 25 × 16.5 cm. G. Doin & Cie, Paris, 1960. Price, NF 54.

Medical Entomology. 5th Ed. By WILLIAM B. HERMS, Sc.D., and revised by MAURICE T. JAMES, Ph.D. 616 pages; 24 × 16 cm. The Macmillan Company, New York, 1961. Price, $12.50.

Medicine Makers of Kalamazoo. By LEONARD ENGEL. 24 × 14 cm. 261 pages; McGraw-Hill Book Company, Inc., New York, 1961. Price, $4.50.

Molecular Genetics and Human Disease. Edited by LYTT I. GARDNER, M.D. 297 pages; 23.5 × 16 cm. Charles C Thomas, Springfield, Ill., 1961. Price, $11.50.

My Friends the Doctors. By SIGMUND L. WILENS, M.D. 245 pages; 22 × 14 cm. Atheneum Publishers, New York, 1961. Price, $5.00.

Pharmacology. The Nature, Action, and Use of Drugs. 2nd Ed. By HARRY BECKMAN, M.D. 805 pages; 26 × 18.5 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $15.50.

Proceedings of the Pneumoconiosis Conference Held at the University of Witwatersrand, Johannesburg, 9th–24th February, 1959; sponsored by the South African Council for Scientific and Industrial Research. Edited by A. J. ORENSTEIN, M.D., D.Sc., LL.D., F.R.C.P. 632 pages; 24 × 16.5 cm. Little, Brown and Company, Boston, 1961. Price, $22.50.

Radiation Protection and Dentistry. By ARTHUR H. WUEHRMANN, D.M.D. 238 pages; 20 × 13 cm. The C. V. Mosby Company, St. Louis, Mo., 1960. Price, $6.50.

Recent Advances in Renal Disease. The Proceedings of a Conference Held in London at the Royal College of Physicians of London, July 22–23, 1960. Edited by M. D. MILNE. 254 pages; 23 × 15.3 cm. J. B. Lippincott Company, Philadelphia, 1961. Price, $5.00 (paper-bound).

The Riggs Story. The Development of the Austen Riggs Center for the Study and Treatment of the Neuroses. By LAWRENCE S. KUBIE, M.D. 182 pages; 21.5 × 14.5 cm. Paul B. Hoeber, Inc., Medical Division of Harper & Bro., New York, 1960.

Smoking: Its Influence on the Individual and Its Role in Social Medicine. By C. VAN PROOSDY, M.D., Zonnestral Hospital, Hilversum, The Netherlands. Elseview Publishing Co., The Netherlands; the D. Van Nostrand Co., Inc., New York, exclusive U. S. Agents, 1960. Price, $11.00.

The Surgery of Mitral Stenosis. Modern Surgical Monographs No. 4. By ROBERT P. GLOVER, M.D., and JULIO C. DAVILA, M.D. 219 pages; 23.5 × 15.5 cm. Grune & Stratton, New York, 1961. Price, $9.50.

Textbook of Medical Physiology. 2nd Ed. By ARTHUR C. GUYTON, M.D., Professor and Chairman, Department of Physiology and Biophysics, University of Mississippi School of Medicine. 1,181 pages; 26 × 18 cm. W. B. Saunders Company, Philadelphia, 1961. Price, $15.50.

Treatment of Emotional Problems in Office Practice. By FRANK F. TALLMAN, M.D. 426 pages; 20.8 × 14 cm. McGraw-Hill Book Company, Inc., New York. Price, $11.00.

Trends in Juvenile Delinquency. World Health Organzation Public Health Papers No. 5. 56 pages; 21 × 14 cm. Published by the World Health Organization, Geneva, 1961. Price, 60¢ per copy (paper-bound).

The Undergraduate Teaching of Psychiatry and Mental Health Promotion. Ninth Report of the Expert Committee on Mental Health. World Health Organization Technical Report Series No. 208. 36 pages; 24 × 16 cm. Published by the World Health Organization, Geneva, 1961. Price, 30¢ per copy (paper-bound).